©CIB 194305

Vol. 25 MAY, 1949 No. 5

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

EDITORS

ALTON OCHSNER, New Orleans OWEN H. WANGENSTEEN, Minneapolis

ASSOCIATE EDITORS

ALFRED BLALOCK, Baltimore I. S. RAVDIN, Philadelphia

PEB

Original Communications

The Healing of the Wound as a Biologic Phenomenon. Samuel C. Harvey, M.D., New Haven, Conn. ---- 655

An Evaluation of Mixtures of Ossein Gelatin, Hydrolyzed Protein, and Glucose in the Parenteral Nutrition of Postoperative Patients. Cecilia Riegel, Ph.D., C. E. Koop, M.D., C. W. Schwegman, M.D., M. T. Barnes, and R. P. Grigger, Philadelphia, Pa. ---- 672

Studies on Burns. III. The Effect of Heparin on the Circulating Blood Plasma and Proteins in Experimental Burns. E. Meredith Alrich, M.D., Charlottesville, Va. 676

A Study of Vehicles and Adjuvants for the Sulfonamides and Penicillin. Edwin J. Pulaski, M.D., Fort Sam Houston, Texas ---- 681

Massive Penicillin Therapy of Abdominal Actinomycosis. Gilman E. Sanford, M.D., and Richard O. Barnes, M.D., Memphis, Tenn. ---- 711

The Effect of Temporary Renal Vascular Occlusion on Kidney Function. J. R. Scheibe, M.D., E. Giraldi, M.D., and C. W. Vermeulen, M.D., Chicago, Ill.-- 724

Dislocations and Fracture-Dislocations of the Foot: Transfixion With Kirschner Wires. Edwin O. Geckeler, M.D., Philadelphia, Pa. ---- 730

(Contents continued on inside back cover)

Published by THE C. V. MOSBY COMPANY, St. Louis, U. S. A.

Copyright 1949 By The C. V. Mosby Company

SURGERY

ADVISORY COUNCIL

DONALD C. BALFOUR, Rochester, Minn.
VILRAY P. BLAIR, St. Louis
BARNEY BROOKS, Nashville
WILLIAM E. GALLIE, Toronto
EVARTS A. GRAHAM, St. Louis
HOWARD C. NAFFZIGER, San Francisco
HARVEY B. STONE, Baltimore
ALLEN O. WHIPPLE, New York City

EDITORIAL BOARD

FREDERICK A. COLLER, Ann Arbor
EDWARD D. CHURCHILL, Boston
VERNON C. DAVID, Chicago
LESTER R. DRAGSTEDT, Chicago
RALPH K. GHORMLEY, Rochester, Minn.
SAMUEL C. HARVEY, New Haven
FRANK HINMAN, San Francisco
EMILE F. HOLMAN, San Francisco
EDWIN P. LEHMAN, University, Va.
FRANK L. MELENEY, New York City
JOHN J. MORTON, Rochester, N. Y.
THOMAS G. ORR, Kansas City, Kan.
GEORGE T. PACK, New York, N. Y.
WILDER G. PENFIELD, Montreal
WILLIAM F. RIENHOFF, JR., Baltimore

COMMITTEE ON PUBLICATIONS

ARTHUR W. ALLEN
Boston, Mass.

CLAUDE S. BECK
Cleveland, Ohio.

ELEXIOUS T. BELL
Minneapolis, Minn.

ISAAC A. BIGGER
Richmond, Va.

ALBERT C. BRODERS
Rochester, Minn.

J. BARRETT BROWN
St. Louis, Mo.

ALEXANDER BRUNSCHWIG
New York, N. Y.

LOUIS A. BUIE
Rochester, Minn.

WARREN H. COLE
Chicago, Ill.

C. D. CREEVY
Minneapolis, Minn.

GEORGE M. CURTIS
Columbus, Ohio

M. DE BAKEY
Houston, Texas

WILLIAM J. DIECKMANN
Chicago, Ill.

DANIEL C. ELKIN
Atlanta, Ga.

WILLIS D. GATCH
Indianapolis, Ind.

CHARLES F. GESCHICKTER
Baltimore, Md.

J. MASON HUNDLEY, JR.
Baltimore, Md.

ANDREW C. IVY
Chicago, Ill.

DENNIS E. JACKSON
Cincinnati, Ohio

J. ALBERT KEY
St. Louis, Mo.

CHAUNCEY LEAKE
Galveston, Texas

FRANCIS E. LEJEUNE
New Orleans, La.

HAROLD I. LILLIE
Rochester, Minn.

JOHN S. LUNDY
Rochester, Minn.

FRANK C. MANN
Rochester, Minn.

CHARLES W. MAYO
Rochester, Minn.

ROBERT L. PAYNE
Norfolk, Va.

LEO G. RIGLER
Minneapolis, Minn.

ERNEST SACHS
St. Louis, Mo.

ARTHUR M. SHIPLEY
Baltimore, Md.

ALBERT O. SINGLETON
Galveston, Texas

MAURICE B. VISSCHER
Minneapolis, Minn.

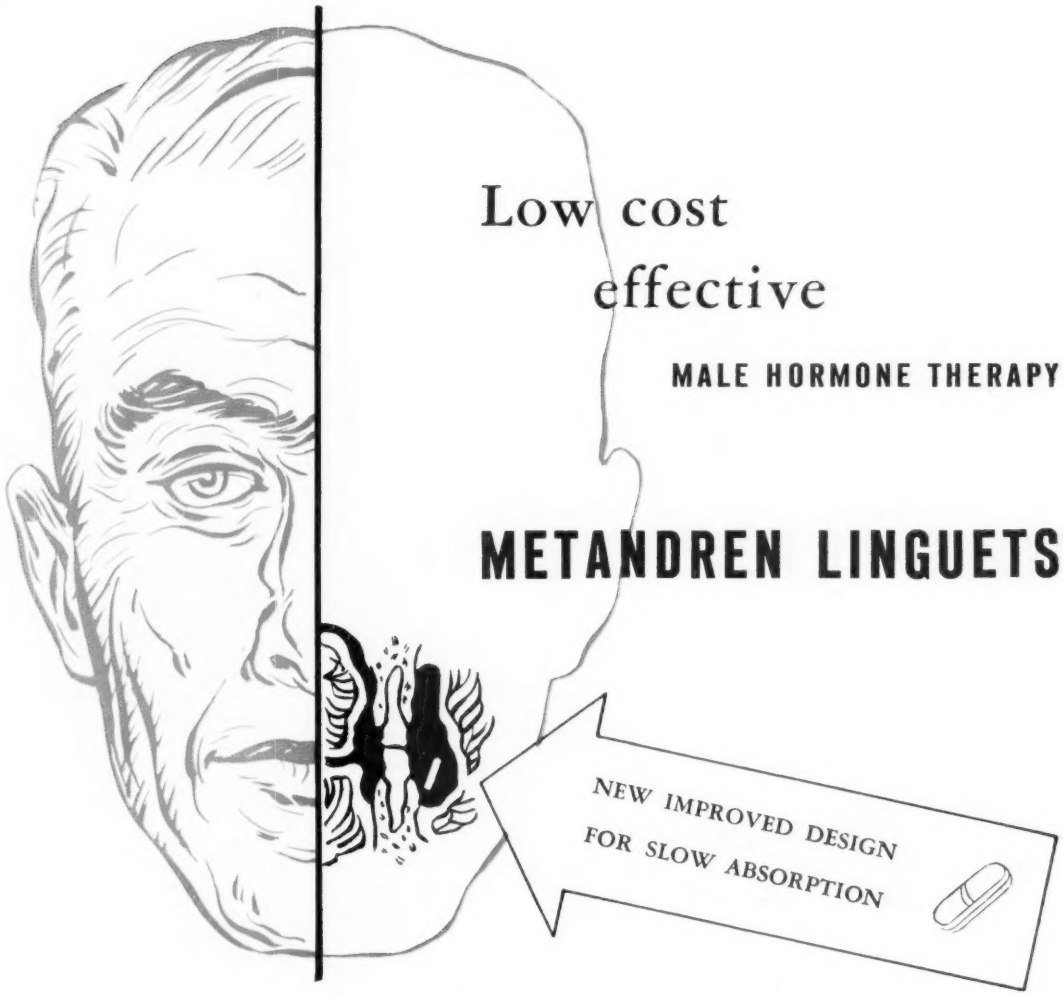
RALPH M. WATERS
Madison, Wis.

JAMES C. WHITE
Boston, Mass.

PHILIP D. WILSON
New York, N. Y.

JOHN A. WOLFER
Chicago, Ill.

Vol. 25, No. 5, May, 1949. Surgery is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its possessions, Pan-American Countries, $10.00 a year; Canada and foreign, $11.00. Entered as Second-Class Matter January 20, 1937, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in U. S. A.



Low cost effective

MALE HORMONE THERAPY

METANDREN LINGUETS

"Much smaller doses of androgen can be given if it is slowly absorbed in the mouth (than by ingestion) as the drug goes directly into circulation, thus preventing large amounts of the drug being destroyed in the liver."[1]

This efficient absorption is made possible by the Metandren Linguet – specially designed to dissolve *slowly* in the space between cheek and gum or under the tongue. As a result, the dosage of methyltestosterone need be only about one-half that required when this male sex hormone is ingested in tablet form.

Adult maintenance dosage is from two to four 5-mg. Linguets daily. Most children need only one-half to one 5-mg. Linguet daily.

- *Literature on request.*

1. Habel, J. M., Jr.: Va. Med. Monthly, October 1948.

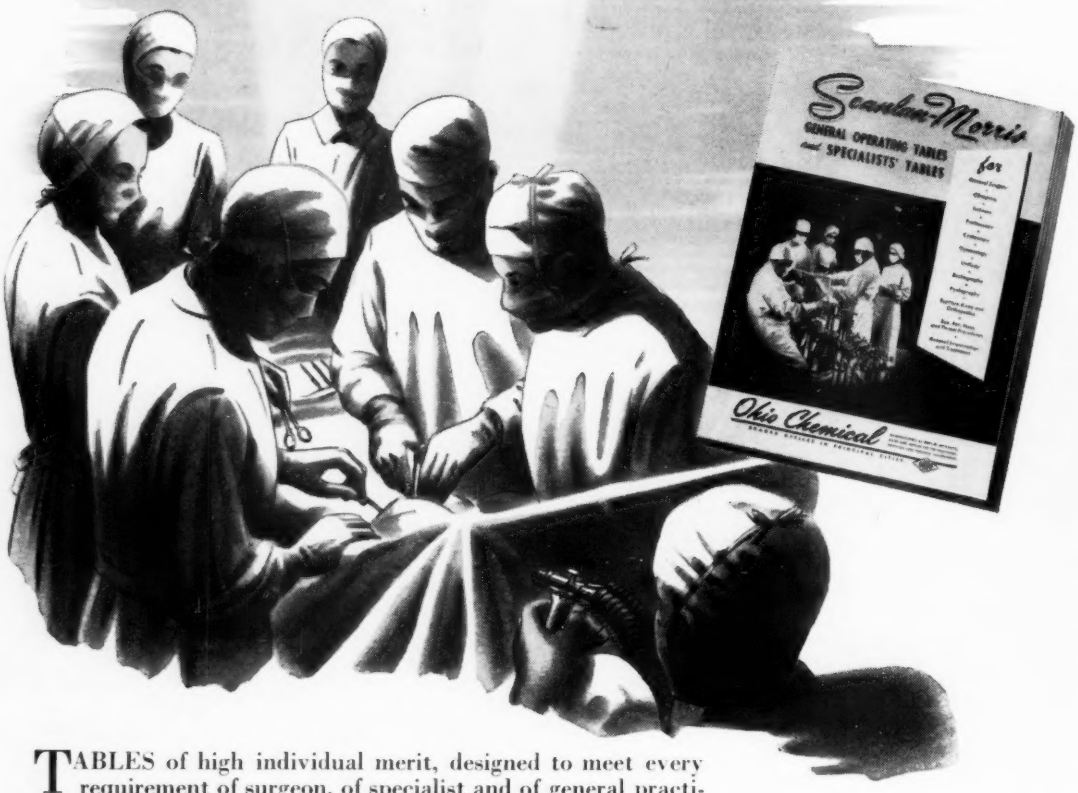
METANDREN LINGUETS, 5 mg. (white) scored; 10 mg. (yellow) scored – in bottles of 30, 100 and 500.

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

METANDREN, LINGUETS — Trade Marks Reg. U.S. Pat. Off. 2/1437M

Tables FOR EVERY OPERATING,

EXAMINING AND TREATMENT REQUIREMENT



TABLES of high individual merit, designed to meet every requirement of surgeon, of specialist and of general practitioner are included in the Ohio-Scanlan line. Noteworthy members are the new hydraulic Ohio-Scanlan A-6000 Major Operating Table with "Selectrol" positioner at the right side, head end, for selection and control of all postures—a table of unequalled convenience, efficiency and dependability; the Sisk Urological X-ray table . . . the Hawley-Scanlan Fracture X-ray and Orthopedic table . . . the Buie Proctoscopic and Examining table . . . the Braasch-Bumpus Urological X-ray table . . . the Nesbit combination table for eye, ear, nose and throat work . . . the Ohio-Scanlan delivery and obstetrical table . . . and an efficient, medium-priced, all-purpose operating table Model A 2003 B suitable for routine surgery and general service. Write for catalog, "Ohio-Scanlan General Operating Tables and Specialists' Tables." For immediate detailed information, call our nearest branch sales office.

OHIO HOSPITAL EQUIPMENT

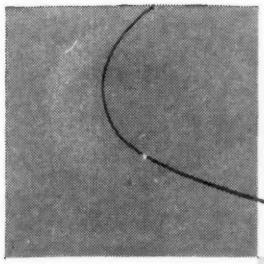
Heidbrink Anesthesia Apparatus Ohio-Heidbrink Oxygen Therapy Apparatus • Kreiselman Resuscitators • Scanlan-Morris Sterilizers • Ohio Scanlan Surgical Tables • Operay Surgical Lights Scanlan Surgical Sutures • Steril-Brite Furniture • Recessed Cabinets • U. S. Distributor of Stille Instruments.

OHIO MEDICAL GASES

Oxygen • Nitrous Oxid Cyclopropane • Carbon Dioxid • Ethylene Helium and mixtures • Also Laboratory Gases and Ethyl Chloride • please return empty cylinders promptly.

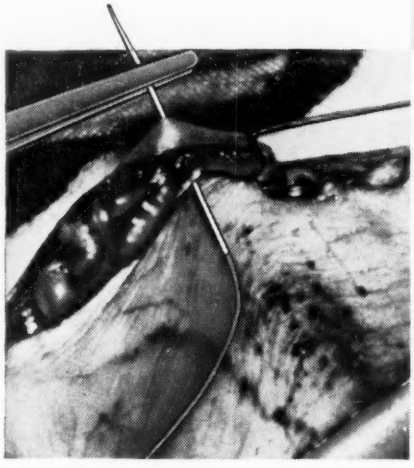
Ohio Chemical OHIO

THE OHIO CHEMICAL & MFG. CO. 1400 East Washington Ave., Madison 10, Wisconsin • Branch offices in principal cities • Represented in Canada by Ohio Chemical Canada Limited, Montreal and Toronto, and internationally by Airco Corporation (International), New York 18.



D & G SUTURES

WITH ATRAUMATIC* NEEDLES



an approach to the ideal

Davis & Geck pioneered the development of the Atraumatic needle principle to meet virtually every situation where minimum trauma is essential. In design and construction, D&G Sutures with Atraumatic Needles approach the ideal more closely than any other combination for these reasons:

1. Needles and sutures are practically the *same* diameter and form a smooth, continuous unit.
2. The method of affixing insures positive anchorage to the suture—it cannot pull out...and its strength is unimpaired at the contact point.
3. Construction of swaged-on portion provides a sleeve of exceptional strength which will not bend or break and has no projecting edges.
4. All curved needles have a flattened area to prevent turning in the needle holder.
5. Each Atraumatic suture-needle combination has been developed in collaboration with recognized authorities and represents the consensus of professional opinion in its particular field.

THE D&G ATRAUMATIC SUTURE-NEEDLE LINE is the most comprehensive line of its type available.

*Registered U. S. Pat. Off.

DAVIS & GECK, INC.

57 WILLOUGHBY STREET BROOKLYN 1, NEW YORK

For mixed infections

FURACIN*†
SOLUBLE DRESSING
(BRAND OF NITROFURAZONE)
CONTAINS 0.2% NITROFURAZONE (5-NITRO-2-FURALDEHYDE SEMICARBAZONE) IN A WATER SOLUBLE BASE.
CAUTION: TO BE DISPENSED ONLY BY OR ON THE PRESCRIPTION OF A PHYSICIAN.
PRESCRIPTION OF PRODUCT AND USES AVAILABLE TO PHYSICIANS ON REQUEST.
AN ANTIBACTERIAL PREPARATION FOR TOPICAL APPLICATION.
LABORATORIES Inc.
NORWICH, NEW YORK
ONE POUND, AVOIR

In malodorous lesions, the wide antibacterial spectrum of Furacin frequently enables it to abate the odor rapidly. Such a benefit has been reported in cutaneous ulcers, diabetic gangrene, abscesses, chronic wounds and ulcerating malignant growths.* Furacin® brand of nitrofurazone, is available as Furacin Soluble Dressing (N.N.R.) and Furacin Solution (N.N.R.) containing 0.2 per cent Furacin. These preparations are indicated for topical application *in the prophylaxis or treatment of infections of* wounds, second and third degree burns, cutaneous ulcers, pyodermas and skin grafts. *Literature on request.*

EATON LABORATORIES, INC., NORWICH, N. Y.

*Downing, J. G. et al.: *Use of 5-Nitro-2-Furaldehyde Semicarbazone in Dermatology,* J. A. M. A. **133**:299, 1947 • Shipley, E. R. et al.: *Clinical Observations on Furacin Soluble Dressing in the Treatment of Surface Infections,* Surg., Gynec. & Obst. **84**:366, 1947 • McCollough, N. C.: *Treatment of Infected War Wounds with a Nitrofuran,* Indust. Med. **16**:128, 1947 • Wawro, N. W.: *Newer Aspects of the Palliative Treatment of Cancer,* Connecticut State M. J. **12**:17, 1948.

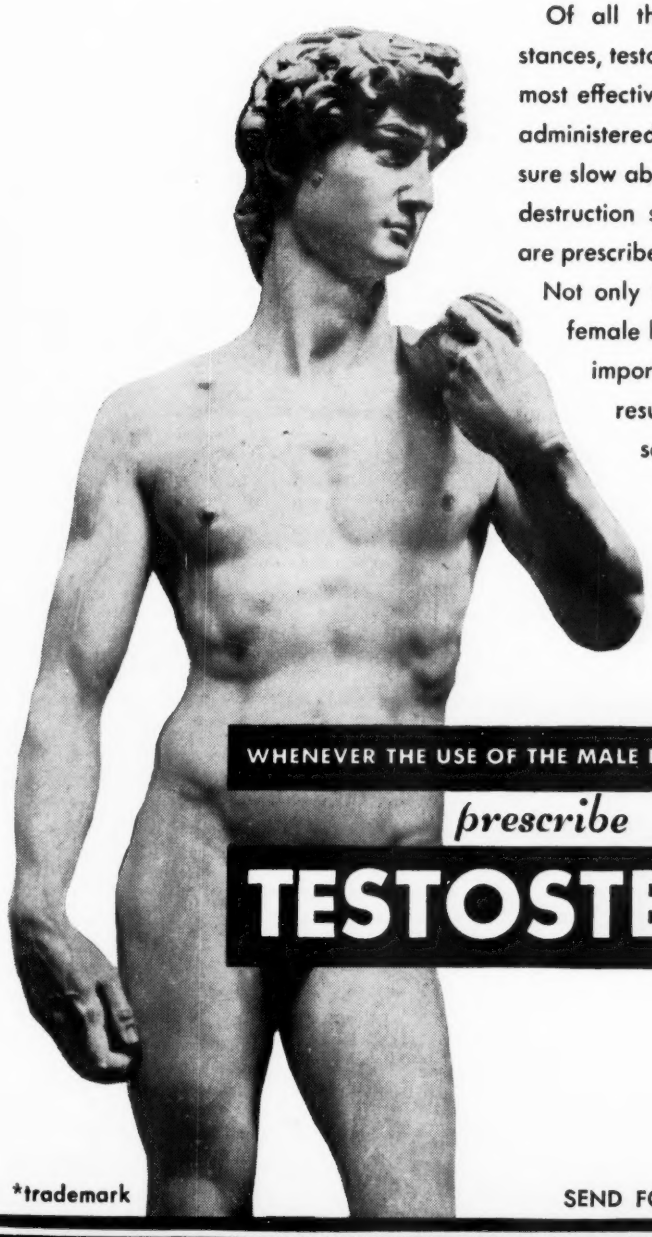
Edocet Experientia

PURE CRYSTALLINE MALE HORMONE—THE MOST POTENT ANDROGEN

Clinical Application

Of all the known androgenic substances, testosterone is recognized as the most effective; particularly is this true if administered under conditions that assure slow absorption and preclude rapid destruction such as when Membrettes* are prescribed for transmucosal therapy.

Not only in the male but also in the female have androgens assumed an important role in recent years. The results obtained have been so satisfactory that the use of free testosterone is becoming increasingly widespread.



WHENEVER THE USE OF THE MALE HORMONE IS INDICATED

prescribe

TESTOSTERONE

Wyeth®

*trademark

SEND FOR ILLUSTRATED BROCHURE

AQUEOUS SUSPENSION	MEMBRETTES+	PELLETS
For Injection Therapy	For Transmucosal Absorption	For Implantation

WYETH INCORPORATED, PHILADELPHIA 3, PA.

SURGERY

Editors: ALTON OCHSNER, M.D., 1430 Tulane Ave., New Orleans, La., and OWEN H. WANGENSTEEN, M.D., University Hospitals, Minneapolis, Minn.

Associate Editors: ALFRED BLALOCK, M.D., Johns Hopkins Hospital, Baltimore, Md., and I. S. RAVDIN, M.D., Hospital of the University of Pennsylvania, Philadelphia, Pa.

Published by THE C. V. MOSBY COMPANY, 3207 Washington Blvd., St. Louis 3, U.S.A.

Great Britain Agents: Henry Kimpton, Ltd., 26 Bloomsbury Way, London, W.C.1.
Entered at the Post Office at St. Louis, Mo., as Second-Class Matter.

Published Monthly. Subscriptions may begin at any time.

Editorial Communications

Original Communications.—This Journal invites concise original articles of new matter in the broad field of clinical and experimental surgery. Descriptions of new techniques and methods are welcomed. Articles are accepted for publication with the understanding that they are contributed solely to SURGERY.

Manuscripts submitted for publication may be sent to Dr. Alton Ochsner, 1430 Tulane Avenue, New Orleans, Louisiana, or to Dr. Owen H. Wangensteen, University Hospitals, Minneapolis, Minnesota.

Neither the editors nor the publishers accept responsibility for the views and statements of authors expressed in their communications.

Translations.—Manuscripts written in a foreign language, if found suitable for publication, will be translated without cost to the author.

Manuscripts.—Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. References should be placed at the end of the article and should conform to the style of the Quarterly Cumulative Index Medicus; viz., name of author, title of article, and name of periodical with volume, page, and year. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked on margin or back with the author's name.

Authors should indicate on the manuscript the approximate position of text figures. The original drawings, not photographs of them, should accompany the manuscript.

Illustrations.—A reasonable number of half-tone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the editors for color plates, elaborate tables or extra illustrations. Copy for zinc cuts (such as pen drawings and charts) should be drawn and lettered only in India ink, or black typewriter ribbon (when the typewriter is used), as ordinary blue ink or colors will not reproduce. Only good photographic prints or drawings should be supplied for half-tone work.

Exchanges.—Contributions, letters, exchanges, reprints, and all other communications relating to SURGERY should be sent to one of the editors.

Review of Books.—Books and monographs, native and foreign, will be reviewed according to their merits and as space permits. Books may be sent to Dr. Owen H. Wangensteen, University Hospitals, Minneapolis, Minn.

Reprints.—Reprints of articles published among "Original Communications" must be ordered directly through the publishers, The C. V. Mosby Co., 3207 Washington Blvd., St. Louis 3, U.S.A., who will send their schedule of prices. Individual reprints of an article must be obtained through the author.

Business Communications

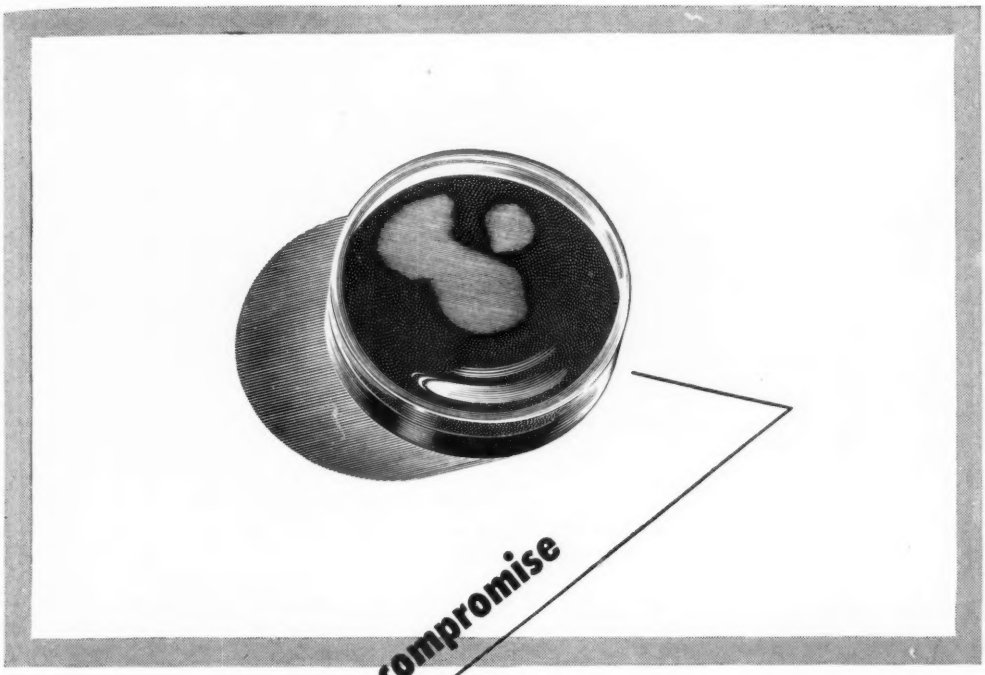
Business Communications.—All communications in regard to advertising, subscriptions, change of address, etc., should be addressed to the publishers, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo.

Subscription Rates.— Single copies, Domestic and Pan-American Countries, $1.10; Foreign, $1.20. In the United States and its Possessions and the Pan-American Countries, $10.00 per year in advance. Canada and other Foreign Countries, $11.00. Includes two volumes a year, January and July.

Remittances.—Remittances for subscriptions should be made by check, draft, post office or express money order, or registered letter, payable to the publishers, The C. V. Mosby Co.

Change of Address.—The publishers should be advised of change of subscriber's address about fifteen days before the date of issue, with both new and old addresses given.

Advertisements.—Only articles of known scientific value will be given space. Forms close first day of month preceding date of issue. Advertising rates and page sizes on application.



Bacteria don't compromise

Nothing less than complete antiseptic action is satisfactory in surgical procedures. That is why such painstaking research preceded the development of Zephiran.

Pick any of the important attributes of a good antiseptic you want . . . prompt effectiveness, economy, safety . . . and you will find it in Zephiran chloride.

Zephiran chloride actually kills bacteria, it doesn't just inhibit them. It's fast in its action, too —faster than many other antiseptics. What's more, Zephiran is adequately germi*cidal* and less toxic than the mercurials.

For an antiseptic that is useful everywhere in hospital and office practice, SPECIFY

ZEPHIRAN® CHLORIDE

EFFECTIVE, SAFE, ECONOMICAL ANTISEPTIC

Winthrop-Stearns INC.

NEW YORK 13, N. Y. • WINDSOR, ONTARIO

Supplied as: Aqueous Solution 1:1000, bottles of 8 fl. oz. and 1 U. S. gallon. Tincture 1:000, tinted and stainless, bottles of 8 fl. oz. and 1 U. S. gallon. Concentrated Aqueous Solution 12.8%, bottles of 4 fl. oz. and 1 U. S. gallon (1 oz.=1 U. S. gallon 1:1000 solution).

Zephiran, trademark reg. U. S. & Canada, brand of benzalkonium chloride (refined).

DESERVES A **MASTER BLADE**

CRESCENT

CRESCENT SURGICAL SALES CO., INC. NEW YORK

NO careful operator tolerates less than the best in blades! That's why so many insist on Crescent.

They're sharper—with cutting edge ground to a longer, flatter bevel.

They're more rigid—incorporating one-third more of the finest surgical steel.

They're better balanced—with weight evenly distributed (no thinning down from the back).

Performance ***in your own hand*** can alone tell the whole story. If you're not yet using Crescent blades, send for complimentary samples—now! Call your surgical dealer . . . or write to Crescent Surgical Sales Co., Inc., New York.

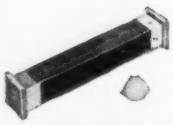
CRESCENT SURGICAL BLADES

Copies Wanted

The publishers will pay 60¢ per copy for these issues of SURGERY.

1942—January, July, August, September, November.
1944—January, June, July, August, November.
1948—January.

Write your name and address plainly on wrapper and address copies to: *A. W. Volland, Circulation Manager, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo.*



SHARPEN Your Own Precision Instruments!

Pratt Handsharpener with Blue Cake!

- Produces keener edges.
- Edges last 3 to 5 times longer.
- No skill required.

ORDER ONE TODAY!
$2.50 postpaid. Money Back Guarantee.
Literature available.

WALDO TODD PRATT
84 Maplewood Ave. W. Hartford, Conn.

Changing Your Address?

WHEN YOU MOVE, PLEASE—

(1) Notify us to change your address—allow us six weeks to make the change.

(2) Mention the name of this Journal. (We publish eleven periodicals.)

(3) Give us your old address. If possible, return the addressed portion of the envelope in which we sent your last copy.

(4) Give us your new address—complete—including the Postal zone number.

(5) Please print your name and address.

Thank You!

Circulation Department, The C. V. Mosby Company, Publishers, 3207 Washington Blvd., St. Louis 3, Mo.

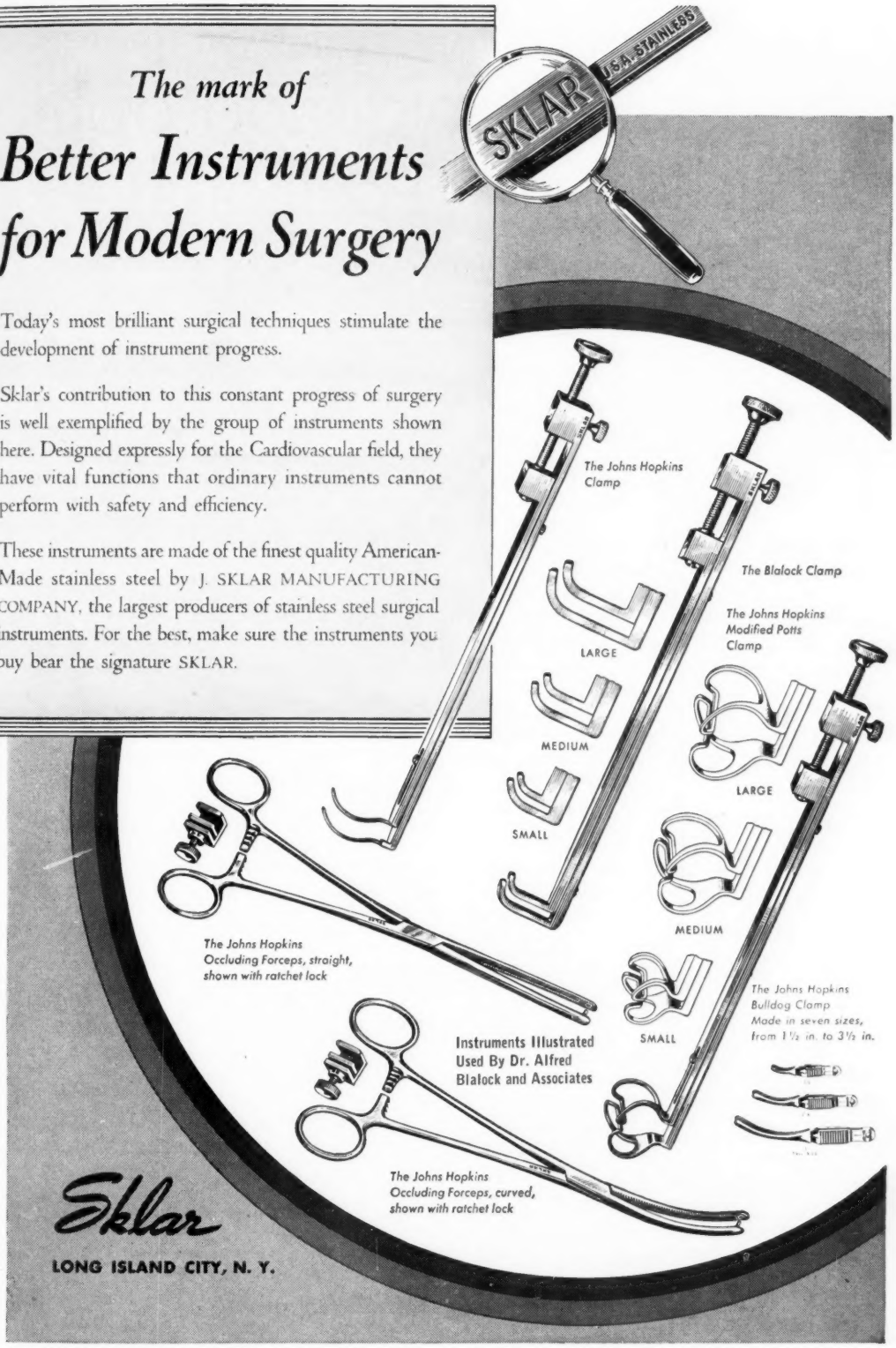
The mark of

Better Instruments for Modern Surgery

Today's most brilliant surgical techniques stimulate the development of instrument progress.

Sklar's contribution to this constant progress of surgery is well exemplified by the group of instruments shown here. Designed expressly for the Cardiovascular field, they have vital functions that ordinary instruments cannot perform with safety and efficiency.

These instruments are made of the finest quality American-Made stainless steel by J. SKLAR MANUFACTURING COMPANY, the largest producers of stainless steel surgical instruments. For the best, make sure the instruments you buy bear the signature SKLAR.


SKLAR
J.S.A. STAINLESS
The Johns Hopkins Clamp
The Blalock Clamp
The Johns Hopkins Modified Potts Clamp
LARGE
MEDIUM
SMALL
LARGE
MEDIUM
SMALL
The Johns Hopkins Occluding Forceps, straight, shown with ratchet lock
Instruments Illustrated Used By Dr. Alfred Blalock and Associates
The Johns Hopkins Bulldog Clamp Made in seven sizes, from 1½ in. to 3½ in.
The Johns Hopkins Occluding Forceps, curved, shown with ratchet lock

Sklar

LONG ISLAND CITY, N. Y.

SKLAR PRODUCTS ARE AVAILABLE THROUGH ACCREDITED SURGICAL SUPPLY DISTRIBUTORS

Just Released!

Atlas of Roentgenographic Positions

By VINITA MERRILL, while Educational Director, Picker X-Ray Corporation.

IN TWO VOLUMES

708 PAGES

OVER 1500 ILLUSTRATIONS

Size 9 x 12"

PRICE $30.00

EVERY KNOWN POSITION IS DESCRIBED AND ILLUSTRATED
INCLUDES PREPARATORY PROCEDURES FOR PROTECTION OF PATIENT AND TECHNICIAN

Roentgenography is a young and rapidly growing profession. The literature has been widely scattered and fairly inaccessible to students and technicians. This has created a great scarcity of qualified courses and most present-day technicians have learned their work in the hard school of experience.

To fill this great need, the Mosby Company is proud to announce publication of the first American literature to contain a complete assemblage of every known roentgenographic position—each position being accurately illustrated and clearly described. Standard positions, as well as unusual or specialized, are included.

Adequate anatomical and medical information is included in each case.
Definitions of roentgenographic terms are presented.
Numerous bibliographic entries, to facilitate further study, are provided.

Miss Merrill has had many years' experience as a medical x-ray technician, both in hospital and office practice. Having worked under the same handicaps as fellow technicians—the same difficulty in finding authentic source material—she understood the problems and did something about them. She has assembled sufficient material between the covers of these two volumes to serve as a practical reference work—providing any x-ray technician with a tool with which to work with skill and intelligence.

Many of the drawings were prepared from actual anatomical specimens, from radiographs, or from the related photographs. Where several similar positions for obtaining an identical projection have been recommended, the least complicated one has been selected for illustration. In many instances, however, several methods for obtaining similar projections are included.

USE COUPON TO ORDER

THE C. V. MOSBY COMPANY, MJ
3207 Washington Blvd., St. Louis 3, Mo.

Please send me Merrill's Atlas of ROENTGENOGRAPHIC POSITIONS—In Two Volumes

The price is $30.00.

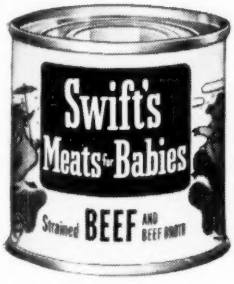
☐ Enclosed find check. ☐ Charge my account.

Name _____

Address _____

Soft-diet patients down in the mouth?

Perk up appetites with Swift's Strained Meats!



6 varieties:
Beef, lamb, pork, veal, liver, heart

Simply putting soft foods on a tray is no assurance that patients will put them away. That's why so many physicians today are recommending Swift's Strained Meats—flavorful, real meats they're sure patients will eat! Prepared specially, soft and smooth, Swift's Strained Meats are so good they tempt even the most apathetic appetites!

Nutritionally, Swift's Strained Meats afford an excellent base for a high-protein, low-residue diet. They're highly digestible—easy to eat. Rich in biologically valuable proteins, they make available simultaneously all known essential amino acids—for optimum protein synthesis. Further, Swift's Strained Meats supply hemapoeitic iron and goodly amounts of natural B vitamins. Let protein-rich Swift's Strained Meats put palatability in menus for your soft-diet patients!

To vary patients' menus, six different Swift's Strained Meats: beef, lamb, pork, veal, liver, heart. Convenient—ready to heat and serve!

The makers of Swift's Strained Meats invite you to send for the new physicians' handbook of protein feeding, written by a doctor, "The Importance of Protein Foods in Health and Disease." Send to:

SWIFT & COMPANY

Chicago 9, Illinois

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

All nutritional statements made in this advertisement are accepted by the Council on Foods and Nutrition of the American Medical Association.

For patients who can take foods of less fine consistency—Swift's Diced Meats offer tender morsels of nutritious meats with tempting flavors patients appreciate.

evidence

DOLOPHINE HYDROCHLORIDE VS. MORPHINE

DOLOPHINE HYDROCHLORIDE (Methadon Hydrochloride, Lilly)	MORPHINE
More effective relief from pain (one-third less drug required)	More euphoria
Less costly	Less suitable for the control of cough

DOLOPHINE HYDROCHLORIDE

dosage:

For moderate pain, 2.5 mg. orally; more severe pain, 5 mg. orally or subcutaneously; very severe pain, 10 mg. subcutaneously. Repeated every four to six hours as necessary.

how supplied:

- Tablets 'Dolophine Hydrochloride,' 2.5 mg., 5 mg., 7.5 mg., and 10 mg., in bottles of 100 and 1,000
- Ampoules 'Dolophine Hydrochloride,' 5 mg., 1 cc., and 10 mg., 1 cc., in packages of 12 and 100; and 10 mg. per cc., in individual 20-cc. rubber-stoppered ampoules
- Syrup 'Dolophine Hydrochloride,' 10 mg. per 30 cc., in bottles of one pint and one gallon
- Powder 'Dolophine Hydrochloride,' in bottles of 15 and 30 grams
- Suppositories 'Dolophine Hydrochloride,' 10 mg., in packages of 12

•Narcotic order required.

Literature on 'Dolophine Hydrochloride' is available to physicians from Lilly medical service representatives or will be forwarded upon request.

ELI LILLY AND COMPANY
Indianapolis 6, Indiana, U.S.A.

SURGERY

VOL. 25 MAY, 1949 No. 5

Original Communications

THE HEALING OF THE WOUND AS A BIOLOGIC PHENOMENON

SAMUEL C. HARVEY,* M.D., NEW HAVEN, CONN.

THE elective wound traversing the protective epithelial covering of the body, and giving access to all parts within, is the fundamental tool of the surgeon. The skill with which he uses it is dependent upon a knowledge acquired empirically for the most part, of the factors which determine the regeneration of the structures disorganized or destroyed by the operative procedure. The injury done is called generically a "wound" and the process of reconstruction, "healing." The healing of a wound has been considered an entity in itself, a peculiar process distinctive to a considerable degree from the other activities of the living organism. It has been thought of as a rude and unusual intrusion giving rise to a specific response which differs in most respects from that which is going on in the body under less striking circumstances.

Primitive man, wounded accidentally or in the course of combat, devoid as he was of any knowledge of the structures or functions of his body, must have been greatly alarmed at first by the bleeding, and later, if he survived, by the "sore" which ensued which healed at times promptly or in other circumstances with delay. The wound differed from other disabilities in that the cause was apparent and required no supernatural rationalization. The first reaction was to apply whatever might be at hand in an effort to control the bleeding and assuage the discomfort. In this way by accumulated experience certain remedies of popular repute became established. Pressure, styptics, organic and inorganic, the actual cautery by the iron or by boiling oil were used to control bleeding, and medicaments without number devised to accelerate healing. The credit for this was usually given to the particular preparation used, rather than to the innate propensity of the wound to heal. Only as man became more rational did he treat bleeding more directly and simply, and also the wound. Paré, in the sixteenth century, not only applied the ligature instead of the cautery in amputations but also simplified

The E. Starr Judd Lecture, University of Minnesota, April 15, 1946.
Received for publication, Oct. 22, 1948.
*Carmalt Professor of Surgery, School of Medicine, Yale University.

the dressing of wounds with a sound understanding, as shown by his well-known expression, "I dressed the wound, God healed it."

The day of the broad generalizations, metaphysically derived, had begun to pass, but it was some centuries yet before the healing of the wound per primam and per secundam as described by Galen ceased to be considered a matter of the "humors" and of "coction." The advances in the attempts at rationalization of the process of wound healing kept pace slowly with the advancing anatomic and physiologic knowledge. With the discovery of the circulation of the blood, the more accurate gross description of the blood vessels, and finally the visualization of the capillary circulation with the microscope, the reaction of the wound healing by secondary intention was supposed to be dependent upon changes in the blood supply. Bleeding and local applications to control this became popular. With the discovery of the lymphatics, John Hunter and his pupils centered their attention on the role of the lymph in the healing of the wound. A healthy agglutination of the wound permitted it to heal per primam while an unhealthy lymph flow prevented this. This concept served for the moment to render more rational the correlation of the character of the exudate with the severity of the inflammation. Incidentally, the gross description by John Hunter of the "granulating wound" still remains unexcelled.

The application by Virchow of the discovery of the cell shifted the attention almost completely from the humoral pathology to the cellular. At the same time the morphologic studies in embryology established the specificity of the cells comprising the various tissues and organs. All of these were highly and permanently differentiated, so much so that for the occasional inconsistencies it was necessary to formulate the terms "dedifferentiation" and "metaplasia."

Meanwhile Cohnheim[1] studied experimentally in animals the initial phase of inflammation in the reaction to injury, and demonstrated elegantly the vascular changes accompanying it, but even more important the emigration of phagocytic cells from the capillaries into the injured tissues. This focused attention on the derivation of these from the bone marrow and subsequently of the monocyte from the reticuloendothelial system of Aschoff and the lymphocyte from the lymphatic apparatus.[2] Even without inflammation or apparent injury these were recognized in various tissues, and some having a constancy of appearance suggestive of differentiation were called the histiocyte. Out of all this came the classical description of the healing of the wound, as presented today in the texts of pathology and surgery, and as given in such great detail in the classical monograph of Marchand.[3] This quite sketchy and superficial history of the subject may serve as a background to the more recent developments.

Previous to these, the observations were qualitative and microscopic by means of which a wealth of information had been obtained. Spain and Loeb[4] first introduced a quantitative approach by counting the number of cells present in a constant area, during the period of repair of a simple, incised wound.

These were epithelial and connective tissue cells and their studies provided a roughly quantitative expression of the rate and character of the cellular changes in this phase of healing. The method is so laborious, however, that the study of a wound with the many variables inherent becomes practically impossible.

Another approach to a quantitative study was that of Carrel and his associates[5] using a surface wound producing a measurable defect in the skin, and the determination of the decreasing surface area, at stated intervals during the process of healing. Under the conditions of this experiment a characteristic graph representing the velocity of healing was established and working with Carrel, DuNoüy devised a mathematical equation to fit it. This perhaps gave a false sense of scientific accuracy, for it was modulated by the introduction of constants to make the equation follow the graph established

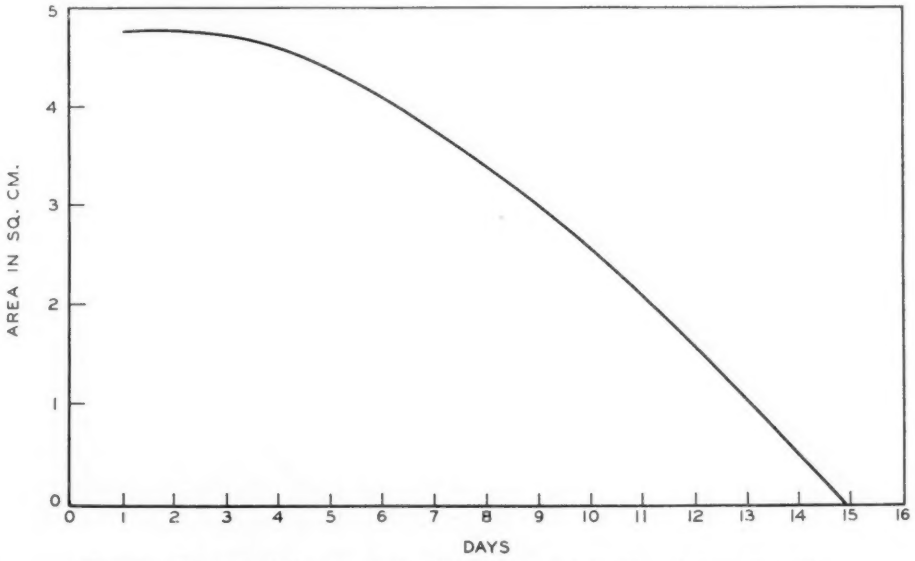


Fig. 1.—Characteristic curve of epithelial wound healing (after Carrel).

by the experiment and was not necessarily applicable in other situations. Certain important information, however, was obtained by these experiments. A latent or lag period of several days preceded the onset of the diminution of the surface area, and at the start, and for several days afterward, the decrease in area was effected for the most part by a process of contracture. It should be noted, however, that the experiment was done in skin not fixed, and other observers working with it attached normally to underlying structures have found that contracture does not occur at all or only to an insignificant degree. Epithelization, when once started, progressed at a velocity inversely as the surface area. In the young animal the velocity of healing was appreciably increased, and in the aged animal it was materially decreased, so that the constant in the equation of DuNoüy had to be adjusted to fit the graph under these circumstances. Working with the poikilothermic animal, the velocity of

the dressing of wounds with a sound understanding, as shown by his well-known expression, "I dressed the wound, God healed it."

The day of the broad generalizations, metaphysically derived, had begun to pass, but it was some centuries yet before the healing of the wound per primam and per secundam as described by Galen ceased to be considered a matter of the "humors" and of "coction." The advances in the attempts at rationalization of the process of wound healing kept pace slowly with the advancing anatomic and physiologic knowledge. With the discovery of the circulation of the blood, the more accurate gross description of the blood vessels, and finally the visualization of the capillary circulation with the microscope, the reaction of the wound healing by secondary intention was supposed to be dependent upon changes in the blood supply. Bleeding and local applications to control this became popular. With the discovery of the lymphatics, John Hunter and his pupils centered their attention on the role of the lymph in the healing of the wound. A healthy agglutination of the wound permitted it to heal per primam while an unhealthy lymph flow prevented this. This concept served for the moment to render more rational the correlation of the character of the exudate with the severity of the inflammation. Incidentally, the gross description by John Hunter of the "granulating wound" still remains unexcelled.

The application by Virchow of the discovery of the cell shifted the attention almost completely from the humoral pathology to the cellular. At the same time the morphologic studies in embryology established the specificity of the cells comprising the various tissues and organs. All of these were highly and permanently differentiated, so much so that for the occasional inconsistencies it was necessary to formulate the terms "dedifferentiation" and "metaplasia."

Meanwhile Cohnheim[1] studied experimentally in animals the initial phase of inflammation in the reaction to injury, and demonstrated elegantly the vascular changes accompanying it, but even more important the emigration of phagocytic cells from the capillaries into the injured tissues. This focused attention on the derivation of these from the bone marrow and subsequently of the monocyte from the reticuloendothelial system of Aschoff and the lymphocyte from the lymphatic apparatus.[2] Even without inflammation or apparent injury these were recognized in various tissues, and some having a constancy of appearance suggestive of differentiation were called the histiocyte. Out of all this came the classical description of the healing of the wound, as presented today in the texts of pathology and surgery, and as given in such great detail in the classical monograph of Marchand.[3] This quite sketchy and superficial history of the subject may serve as a background to the more recent developments.

Previous to these, the observations were qualitative and microscopic by means of which a wealth of information had been obtained. Spain and Loeb[4] first introduced a quantitative approach by counting the number of cells present in a constant area, during the period of repair of a simple, incised wound.

These were epithelial and connective tissue cells and their studies provided a roughly quantitative expression of the rate and character of the cellular changes in this phase of healing. The method is so laborious, however, that the study of a wound with the many variables inherent becomes practically impossible.

Another approach to a quantitative study was that of Carrel and his associates[5] using a surface wound producing a measurable defect in the skin, and the determination of the decreasing surface area, at stated intervals during the process of healing. Under the conditions of this experiment a characteristic graph representing the velocity of healing was established and working with Carrel, DuNoüy devised a mathematical equation to fit it. This perhaps gave a false sense of scientific accuracy, for it was modulated by the introduction of constants to make the equation follow the graph established

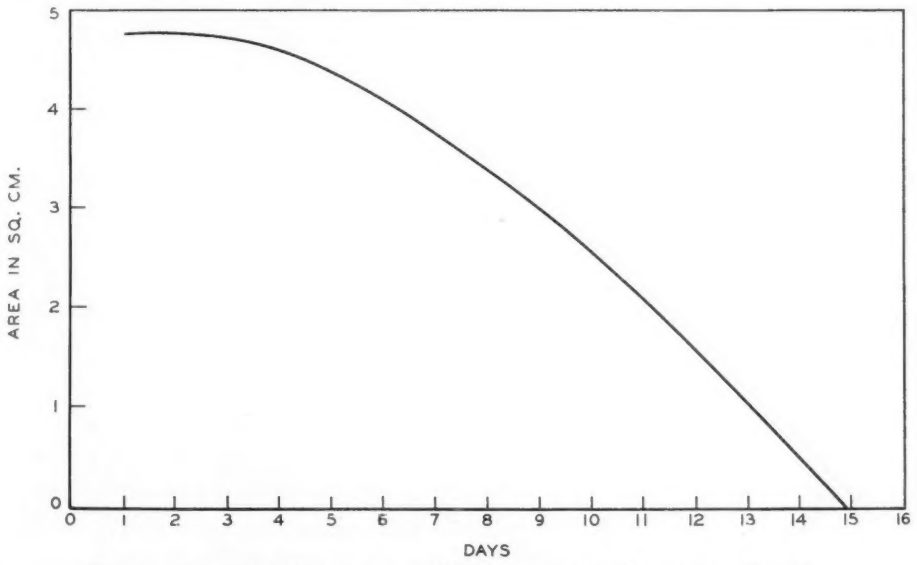


Fig. 1.—Characteristic curve of epithelial wound healing (after Carrel).

by the experiment and was not necessarily applicable in other situations. Certain important information, however, was obtained by these experiments. A latent or lag period of several days preceded the onset of the diminution of the surface area, and at the start, and for several days afterward, the decrease in area was effected for the most part by a process of contracture. It should be noted, however, that the experiment was done in skin not fixed, and other observers working with it attached normally to underlying structures have found that contracture does not occur at all or only to an insignificant degree. Epithelization, when once started, progressed at a velocity inversely as the surface area. In the young animal the velocity of healing was appreciably increased, and in the aged animal it was materially decreased, so that the constant in the equation of DuNoüy had to be adjusted to fit the graph under these circumstances. Working with the poikilothermic animal, the velocity of

healing was a function of the temperature of the subject and with increase of this the velocity was likewise increased in the ratio established for the change of a chemical reaction with an increasing temperature. Occlusion of the wound delayed or completely inhibited the process of healing, while the application of an irritant such as turpentine accelerated it. The most marked retardation of healing was caused by infection, and the open surface wound whether experimental or otherwise requires the utmost care to prevent this.

This was the main variable of Carrel's experiments, but others also obtained. The surface of the wound may be exposed to excessive dryness or humidity, to loss of fluid, to exchange of gases such as absorption of O_2 and loss of CO_2, changes in acidity and alkalinity, and subject to irritation by mechanical or chemical agents, as demonstrated by Carrel himself. The use of antiseptics, such as Dakin's solution to ensure sterility, sets up an artificial situation while in the absence of some such treatment bacterial growth may interfere with the validity of the experiment. Moreover, two major elements enter into the healing of the surface wound as demonstrated by Carrel, the contracture and the epithelial spread.

It is obvious that a closed wound, that is to say, one in which the continuity of the protective epithelial covering is immediately restored, would obviate at once many variables and enable one to confine the study to the element of fibroplasia. The holding power of a wound, that is to say its tensile strength, is almost entirely a function of the number of fibroblasts and their maturation. Even in the dermis, the connective tissue elements rather than the epithelium provide the tensile strength. Therefore, in our laboratory some years ago, a series of experiments was instituted to determine the velocity of healing as determined by the tensile strength of the experimental wound.[6] These were first carried out on the dog and a rough graph was constructed which demonstrated the desirability of further developing the experiment. It was found that the velocity of healing in terms of tensile strength was the same for the various soft tissues and for all the common laboratory animals. This corresponded to the clinical experience in man. It soon became apparent, however, that the use of the larger and more expensive animal, the dog, involved difficulties which made a sufficiently rigorous experiment well-nigh impossible, a matter which some subsequent investigators have overlooked. One experiment, it was found, should extend over fourteen days and required, therefore, the sacrifice of fourteen animals. Quite aside from the cost of this, it was impossible to get such a number of dogs who were of the same breed, age and condition. Moreover, the methods of testing for tensile strength have inherent errors which are not inconsiderable, and with experience it became apparent that for each day it was necessary to sacrifice some four to six animals in order to obtain data significantly reliable. It was decided then to use the rat, an animal which has been for many years standardized as a laboratory animal and whose dietary requirements are well known. Moreover, these can be readily obtained at any desired age.

It was necessary to devise some method for the determination of tensile strength other than a direct mechanical pull because of the lack of sufficient available tissue in so small an animal. This was done by employing the stomach, into which an incision was made, the abdomen being opened for this purpose. The wound in the stomach was approximated with a single running suture of the finest plain catgut, which normally disappears in two to three days and has little if any effect upon the healing process. In testing the tensile strength the stomach was removed with the adjacent esophagus and duodenum. One of these was tied off and the other intubated and connected with a recording manometer. Air was then introduced into the stomach at a constant rate of flow until the wound or the stomach burst under the increasing pressure, the end point being recorded on the kymograph and interpreted in terms of the elevation of a column of mercury. This method has a satisfactory degree of reliability and has been employed by others[7] in the peritoneal cavity for determining the tensile strength of the healing wound in the abdominal wall. From very many observations it was possible to construct with a considerable degree of accuracy a graph representing the tensile strength of a wound, as plotted against time, this being, therefore, a representation of the rate or velocity of healing.*

There is for approximately four days no increase in tensile strength above that provided by the suture which is destroyed in about two days and the agglutination of the two surfaces of the wound by the fibrin formed in the clotting fluid released by the injury. At the end of this latent or lag phase the tensile strength starts to increase rapidly and continues to do so with a diminishing velocity until it reaches a maximum strength in twelve to fourteen days, the greater part of this being achieved in eight to nine days. In the stomach in from ten to twelve days the break in the wall begins to appear elsewhere than in the wound, so the further observations are not of value. The broad cicatrix is then stronger than the relatively thin submucosal layer of connective tissue in which, as Mall and Halsted[8] showed, rests most of the strength of the gastric and intestinal walls. However, if one transfers the experiment to structures with high tensile strength such as skin, tendon, and bone, one finds that this initial phase, which is almost explosive in character, is followed by a secondary phase of increasing strength extending over weeks rather than days, eventually likewise reaching a point where the strength of the healed wound is greater than that of the normal tissue. There are, then, three phases of the increase in tensile strength, the first that of the "lag period," the second that of rapidly increasing tensile strength, and the third that of slowly increasing tensile strength.

It is necessary for further understanding of these phenomena to correlate them with what is otherwise known of wound healing. For the most part this information has been gained by studies in microcytology, and to a

*Were anything to be gained, an equation could be constructed to fit this curve, but it would show nothing not apparent on the graph and should not be used as a control formula for experimentation; every experiment must be done with its own controls, for unforeseen variables may enter which would not be expressed in a master equation.

lesser degree by chemical observations, or perhaps it is more truthful to say by inference from what is known of chemical reactions that may take place under certain conditions. A complete and detailed review of these fields, the literature of which is alike exhaustive and exhausting, is impossible in any limited presentation, but the main and cogent material may be touched upon.* The lag period is characterized by the phenomena associated with the immediate reaction to injury, and in its essentials does not differ in the wound from that occurring from whatever cause in any part of the body. It is a comparatively simple and conspicuous instance, but is in no sense a definitive entity peculiar to itself. Knowledge gained from study of other injuries is applicable to the wound and anything that one may learn from the investigation of the reaction to it may well find its application in other situations.

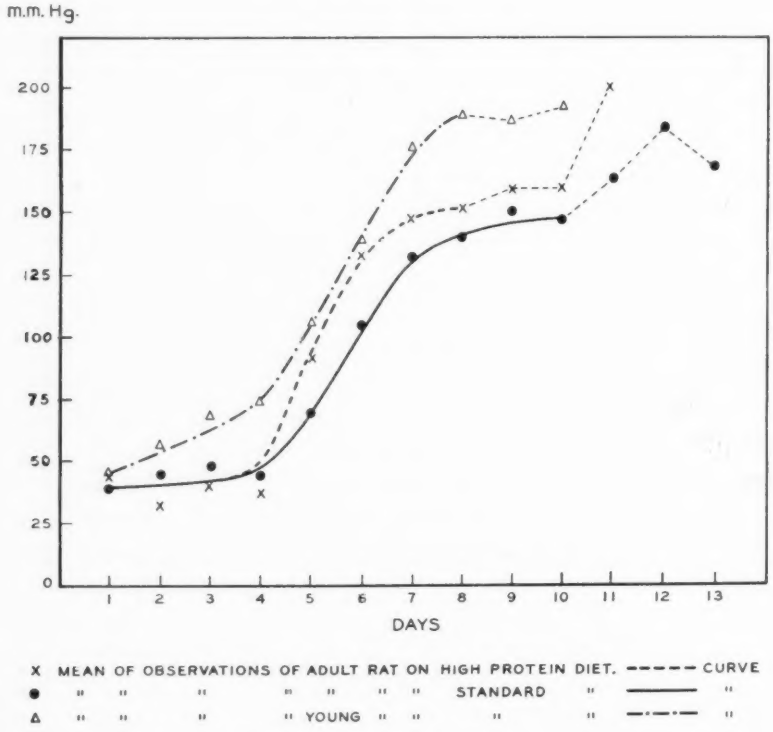


Fig. 2.—Curve of tensile strength of wounds in adult and young rats on standard diet and adult rats on high protein diet.

The initial factor in the onset of the process of the healing of the wound is mechanical damage which, aside from direct injury to the cells of the tissue involved, disrupts the structural and functional equilibrium in which they normally exist. One may assume for the purposes of illustration an entirely

*In doing this, one inevitably falls into a teleologic approach, for while observations and experimentation may and should be done without respect to a supposed purposeful train of events, the integration of the results of these forms a continuity establishing a result obviously essential or desirable from our viewpoint and is therefore in a sense teleological. Life of an individual or of a species is dependent upon certain fundamental processes, and the reaction to injury is one of these, for without this, most organisms would not long survive.

hypothetical example where the cell is separated mechanically from its surrounding environment, that is to say, from contiguous cells and the intercellular medium, and the latter replaced by air. It is at once apparent that the cell under these conditions will not be viable, for it will have its normal interchange of O_2 and CO_2 deranged and will lose rapidly from its surface, water, electrolytes, and other constituents of its cytoplasm essential to its continuing existence. Shortly the entire cell will disintegrate including its nucleus, and in this process there will be a degradation of its protein components as a result of the disordered action of its intrinsic enzymes, the so-called autolysis. Assuming that only one-half of the cell is so exposed, and that the other half remains in its normal environment and that it undergoes the same process, then the adjacent cells will be disturbed to a lesser degree, the effect traveling outward like a wave from a stone dropping in water and diminishing in intensity as it does so, this forming a field of disturbed equilibrium. When the cell is directly injured, this process proceeds even more rapidly and, if it involves many cells, much more extensively. In addition, blood and lymph spaces are transected and even those not directly injured become pervious to their contents to a greater or lesser degree, thus adding their fluids, changed in character by this transition, to the cellular debris. These products of protoplasmic disintegration act as "evocators," to use a sufficiently general embryologic term, and the phagocytic leucocytes derived from the blood appear almost at once in the field as scavengers of the nonviable material, themselves disintegrating concomitant with an increase of the hydrogen ion concentration, and being replaced in considerable part by the macrophagic monocytes and histiocytes which can exist and multiply in a more acid medium. Provided the injury is not a continuing one, as when foreign material difficult of digestion is present in quantity, such as catgut, necrotic masses of tissue, blood, or pathogenic bacteria, this phase is fairly well completed in the lag period of three to four days.

The initial steps in the reparative phase overlap by one or two days the lag period, the fibroblast appearing in small numbers, and then increasing rapidly until by the fourth day their presence is shown in the beginning increases of tensile strength. Their origin and their relation to monocytes and histiocytes, which function as macrophages, are still controversial and perhaps resemble the arguments regarding the relationship of the various members of the primate family which can be best answered by saying that they all arise from a common stem. However this may be, continuation of the exudative reaction defers the appearance of fibroblasts and stretches out the lag period. When this is prolonged, as in abscess formation, in the intermediate zone between the phagocytic cells and the normal surrounding tissues there appears to be a gradation from within outward of monocytes and histiocytes and then fibroblasts, so that the process in the more chronic stages produces an encircling fibrotic wall. This is seen most strikingly in the formation of the tubercle where the acute phagocytic phase is transitory leading to caseation and this is in turn surrounded by monocytic, epithelioid, and giant cells,

and by a capsule of fibrous tissue in all of which the transition from one to the other is not sharply demarcated. The "evocator" action of the foreign substance, whether originating directly within itself or secondarily by destruction of the living cells of the host, varies in type and intensity and induces the common stem cell to proliferate and differentiate into the various forms seen in the reaction to injury.

In the surgical wound which is not infected, the delay in this transition from an exudative to a productive reaction is most commonly caused by damaged tissue as the result of rough handling, exposure to drying, the deprivation of the tissue of its circulation by mass ligatures, the presence of hematoma, or the accumulation of serum because of inadequate hemostasis and approximation of the wound, and lastly the introduction of an unnecessary amount of suture material. This is particularly the case with the absorbable type and involves the rapid disintegration of protein with the evocation of an exudative reaction.*

The shortening of the lag period below that indicated in terms of the onset of the increase of tensile strength is probably not possible, and if it were, is not important, for the greater part of it is involved in the "clearing up process" in the wound. Could this phase be expedited and the mobilization of the fibroblast advanced, there would still remain a very appreciable lag. In fact, in one situation this occurs as demonstrated in our studies on the tensile strength of the healing wound. Young rats still in the period of active growth were selected and the experiment previously described was carried out. It was found that under this circumstance the lag period was diminished by approximately one day or 25 per cent, but that when fibroplasia was once established, there was no change from the adult in the velocity of the proliferation and maturation of the fibroblast. It is known that in cultures of unicellular organisms such as bacteria, which are in a dormant phase, there is an appreciable lag in the multiplication of these on transplantation, while with organisms transferred in an actively growing phase, this lag is materially diminished. This would seem to indicate that in the actively growing animal there is a greater depot of the parent cells for active proliferation. These, like the epithelium on the surface wound, probably flow initially into the wound along the strands of fibrin as they do in culture in vitro, and this movement as well as cell division is presumably expedited in the growing animal. This corresponds, of course, with the clinical impression that wounds heal more rapidly in man during the period of growth, but until rejuvenation becomes possible, it does not seem likely that the surgeon will have available any method for expediting the onset of fibroplasia; he should rather expend his energy in preventing delay by avoiding the complications which may induce it.

Once fibroplasia has proceeded to the point where the tensile strength begins to rise, it becomes apparent on inspection of the graph that it proceeds

*The size of the suture should be determined by the holding power of the tissue in which it is inserted and not by the breaking strength of the surgeon. A suture, whatever its nature, rarely requires a strength greater than that necessary to sustain a pull of 3½ pounds.

with a constantly decreasing velocity. Previous to this time, a matter of two or three days, one can only surmise the course of the curve. Judging from growth curves in general, particularly of the growth of a population in a culture of unicellular organisms, there is an initial period of increasing velocity so that the total graph as extrapolated would be a sigma of which the accelerating phase would be relatively short and the decelerating phase relatively long, perhaps in a ratio of the order of 1 to 3.

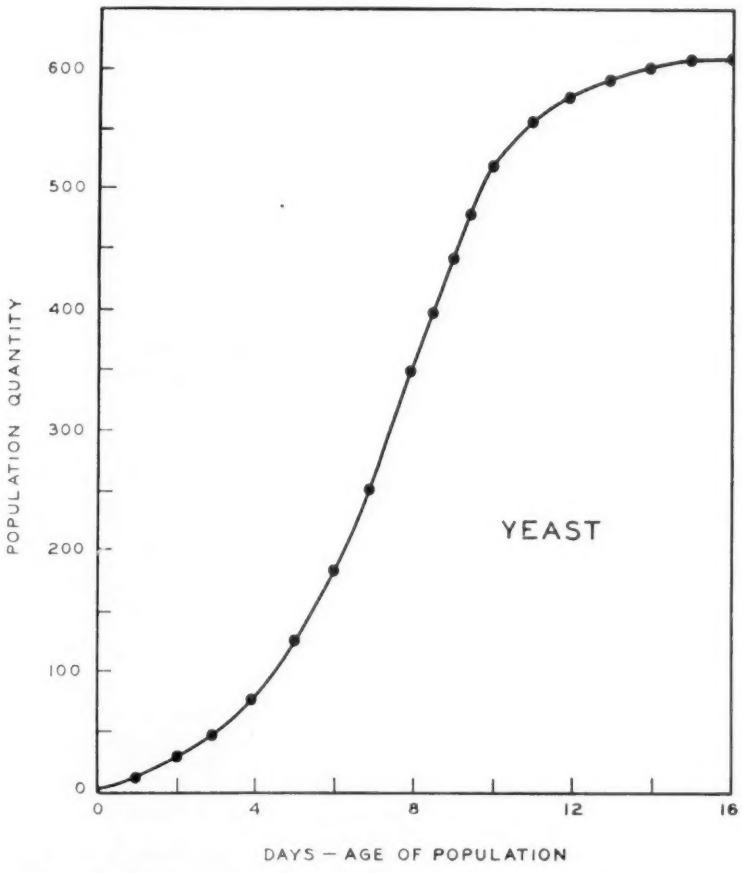


Fig. 3.—Growth curve of yeast population (after Brody and Pearl).

However this may be, it is certain that when the tensile strength becomes measurable, either the stimulating agent or agents is diminishing in proportion to the increasing number of cells, or the inhibitory factor or factors which serve to limit the extent of the growth are progressively coming into play, or possibly a combination of the two. There is no direct evidence to the point, but there is some information which may have an indirect bearing. An implanted growth of fibroblastic tissue in a culture in vitro grows into a colony of a certain size and then comes to rest. A simple incision into this will activate growth again, suggesting that the initial "evocator" had ceased to act, and is reactivated by the procedure.[9] Moreover, an extract of embryonic

tissue will do likewise, and from irradiated yeast cells in a relatively quiescent growth phase, an extract can be obtained which will reactivate their growth.

On the other hand, repeated stimulation of this type does not continue to sustain growth indefinitely in either instance, even if sufficient pabulum is provided and the waste products are removed, unless the menstruum is increased in ratio to the growth, for the cells or the unicellular organisms otherwise reach a certain congestion at which further growth is arrested or inhibited. The factors involved here are not clear, but the fact may be restated in general terms by saying that there is a density of population at which cells cease to grow which bears some relationship to the specific cell involved and in the multicellular organism to its degree of differentiation. To go farther than this carries one into conjecture, but certainly the factors underlying the acceleration and deceleration of growth and of differentiation and regeneration are fundamental to an understanding of embryology, and no less so of the reaction to injury and of the uncontrolled growth of neoplasms.

In any case, the decelerating curve of tensile strength has within itself two phases, the one in which the multiplication of the fibroblast is dominant and the other where its maturation is more significant. This is apparent in correlative histologic studies where there is seen a progressive increase of collagen and a concomitant decrease in the number of immature fibroblasts. Confirmatory evidence has been obtained experimentally.

It is well understood that the primary effect of a deficiency in ascorbic acid is the disappearance of collagen from the tissues, and that this can be best demonstrated in the guinea pig which like man is unable to synthesize this acid.[10] Advantage was taken of this and an experiment set up in this animal in which a severe deficiency was produced, and the tensile strength graph established under these conditions. This showed a significantly lower tensile strength throughout the phase in which collagen is normally formed. Deficit of one of the accessory food factors, then, has a definite and unfavorable effect on the tensile strength of the healing wound, as was strikingly shown in the clinical experiments of Crandon and associates.[11] What the situation may be regarding other accessory food factors has not been tested in this laboratory, but a survey of the literature, which is voluminous, shows no convincing evidence. The observations have beeen made in the clinic and in animals with open surface wounds, in which the variables are many and unpredictable and the data obtained not significant or difficult to interpret with any degree of reliability. Still more intangible and an *ignus fatuus* is the so-called "wound hormone." Again the observations in regard to the various extracts of the many tissues and organs have been on surface wounds of the patient or the experimental animal and subject to the same criticism as is the case with vitamins. The term itself is deceptive in its specificity and should not be used, for it tends to an assumption of knowledge which is not at hand. It is probably true that mildly irritative substances may serve to stimulate growth perhaps by slight injury to the cells, thus liberating a growth-promoting substance, but this is all very intangible and rests upon no solid

evidence. Carrel thought that turpentine had such an effect experimentally, and clinical experience with tincture of myrrh and balsam of Peru tends to bear this out, but no weight can be placed on these observations and, if true, the mechanism remains completely unknown.

Much more tangible are the relationships of the main foodstuffs to the healing of the wound. These have been tested by the tensile strength method in our laboratory, and within the limitations of the experiment have been definitive. First, the rats so used were deprived of all food throughout the course of the acute experiment, with no deviation from the normal curve of healing. Only when the test was made with actively growing young rats was

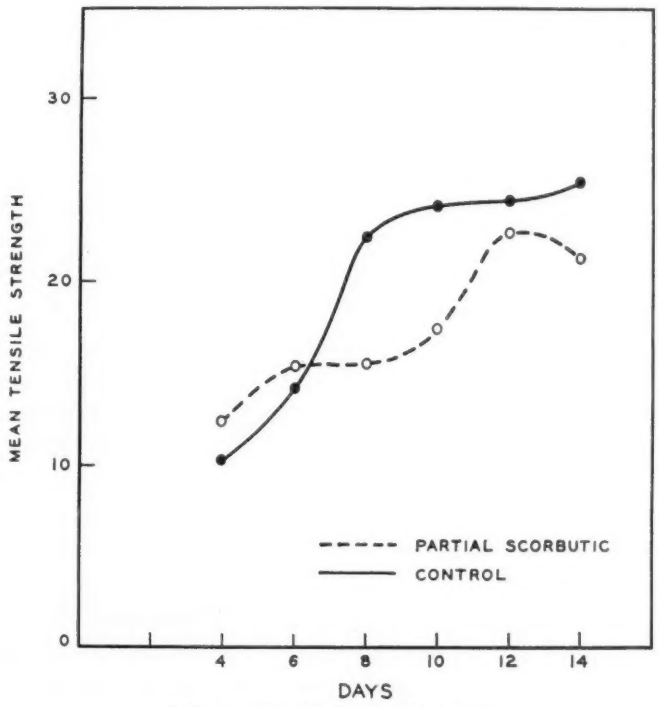


Fig. 4.—Partial scorbutic group.

there some slowing of the velocity, and this, although significant, was insufficient to be of any considerable importance. It must be borne in mind that these experiments were on animals in good nutritional balance, and that the lack of nutrition prevailed only during the course of the experiment, some twelve to fourteen days. Of course, this corresponds to clinical experience, but is nevertheless of theoretical interest. Many years ago it was shown (Morgan, 1906) that in the salamander, deprived of food, the amputated tail regenerated normally, though the animal lost weight severely during the process. This suggests strongly that the process of regeneration has a priority over the maintenance needs of the body otherwise, save where active growth is in progress, in which case our experiment would imply that the

general and the local growth make equivalent demands upon the organism as a whole.

Having determined that adult rats healed under starvation at a normal rate as measured by the tensile strength, diets of adequate caloric value were fed throughout the experiment, but with most of the energy provided in one group by protein, in a second by fat, and a third by carbohydrate. The high carbohydrate diet gave a normal curve, the high fat diet suggested some lowering of the rate but scarcely significantly so, while the high protein diet definitely increased it. In the latter case the lag period remained the same but the velocity of increase of the tensile strength was significantly elevated above that of the normal so that it reached the same level as an end point, about two days earlier. Exactly why this is the case is not known, but it may be recalled that it is well recognized that the ingestion of protein increases the rate of metabolism, the so-called dynamic action of protein (Rubner). It should be borne in mind that while this is valuable evidence of a beneficial effect of a high protein intake, a complete absence of protein during this experimental period did not alter the normal rate of healing. This is said in no sense as questioning the present opinion regarding the advisability of a high protein intake and the undesirability of diminished protein in the body, for which there is ample evidence otherwise, both clinical and experimental.

Again, I must emphasize that these experiments dealt with normal animals, their abnormal diets lasting only for the duration of the acute experiment. The results might be quite different on animals who were subject to a chronic deficiency, and the experiment with ascorbic acid deficiency is an example of this. During the acute starvation there is not time for a serious deficiency to take place even were the guinea pig not capable of synthesizing vitamin C, but with a deficiency well developed by a chronic lack of ascorbic acid the experiment shows a characteristic change in the curve of the healing wound.

So far we have been discussing the healing of the simplest type of wound in which attention has been centered on the proliferation and maturation of fibroblasts, because of the ease of its mensuration and the fact that it is in most circumstances the major component of the healing process. This is a basic reaction to injury of the mesenchyme and of the structures derived from it, and this discussion because of its brevity must be limited to these. The regeneration of the structures derived from the embryologic ectoderm and entoderm cannot, therefore, be considered. Nevertheless, there are certain relationships between these processes that should be touched upon.

In general, the more highly differentiated the cell, and this seems to mean the development of its functions along lines other than mechanical, the less ability it has for regeneration. As in most generalizations there are exceptions to this, but it is strikingly true that certain highly differentiated cells of the central nervous system never regenerate, while epithelium of the skin likewise derived from ectoderm constantly does so throughout life. It is also generally true that the cells derived from the mesoderm are in this sense less

highly differentiated, their functions being for the most part mechanical. It is also true, with but few exceptions, that when both mesodermal cells and those more highly differentiated derived from the ectoderm and endoderm are involved in regeneration, the latter are likely to be outpaced by the former. Wounds of the parenchymatous organs in which both epithelial and mesenchymal derivatives are represented as in the liver or the kidney are prone to effect a repair by the formation of connective tissue rather than by a regeneration of the functional cell peculiar to the organ. This restores structural continuity of the organ at least, and where the function of the injured tissues is mechanical a restoration of both structure and function is achieved. This process of mesenchymal repair is then basic in the reaction to injury of whatever kind and wherever it may occur and follows the pattern previously described.

The clearing away of nonviable material and the fibroplasia taking place under the circumstances of an incised wound takes something less than two weeks, and results in a mass of tissue consisting of proliferating vessels and relatively mature fibroblasts, which is functionally disorganized when one considers its function simply that of occupying space. In many respects this is analogous to the *blastema* well known to the experimental embryologist, and corresponds to the "granulation" tissue of the surgeon. It forms the inner layer of the resolving abscess or hematoma, and surrounds irritating foreign bodies, but most characteristically appears as the bed of the open surface wound. When this occurs under circumstances where the cellular mass is out of equilibrium in the sense that at one plane there is an uncovered surface, growth continues to occur there until the equilibrium is restored usually by obliteration of space by the growth itself or by its becoming otherwise covered. In the open surface wound this is accompanied by contracture probably resulting from the maturation of the proliferating fibroblasts, and is obviated by the ingrowth of epithelium. If the granulation tissue is covered by an impermeable membrane, whether viable or otherwise, it ceases to grow and contracture does not occur. The argument for early skin grafting or, in lieu of this, a nonirritative and occlusive dressing is apparent.

In this respect, a consideration of the blastema previously referred to is instructive. In the tadpoles, on amputation of a limb or the tail, the appendage is regenerated, and the velocity of regeneration measured in terms of mass follows a curve of growth similar to that of the tensile strength of the regenerating wound.[12] This phenomenon has been extensively studied experimentally by those investigators working in the field of developmental zoology and the information there obtained is directly transferable to the healing wound. In the amputation stump is formed the blastema, which is composed of embryonal, mesenchymal cells, which are pluripotential and during the regeneration of the limb differentiate to form all the adult structures in the new limb which in the embryo may arise from the mesenchyme. If skin is removed from elsewhere and transplanted over this, growth ceases, but if the skin of the stump is permitted to grow over the blastema, which it does

rapidly, this acts as an inductor and the regeneration of the limb proceeds. One may, I think, legitimately presume that the cells initiating the regeneration in a wound comprise a blastema which likewise is pluripotential and, under the induction of the field in which it grows, may give rise to various tissues embryonically derived from mesenchyme, although in man the potentiality is somewhat more restricted than it is in the amphibian, which can regenerate and organize a complete and intricate structure such as the tail or a limb.[13]

The phase of maturation of the fibroblast is the beginning of differentiation of the cell, and this overlaps the onset of the phase of organization of the new structure into its ultimate form and function whatever these may be. When this is merely that of a scar, the cells and the collagen become arranged in general in sheaves parallel to the lines of stress arising in the contiguous structures. Where the healing of more well-developed structures is involved as is the case in that of interstitial connective tissue, this becomes more formal in arrangement and comes to approximate in architecture and performance that of the original. This reorganization as contrasted with the initial regeneration may continue a long time before it is completed. One of the simplest illustrations of this is the regeneration of fascia where a defect of some size has been made by excision, of which the dura may be taken as an example.[14] This in the period of eight to ten days is filled in with a sheet of connective tissue in which the cells and the contiguous collagenous fibers run in all directions. In a month what is to all appearances a new dura has been formed which grossly and microscopically closely resembles that of the original membrane. A more highly organized structure is the tendon which on section separates for a variable distance even when sutured, under the pull of the tonus of the attached muscle.[15] This space fills with a blood clot or serum which then passes through the preliminary phases of exudatory reaction and of regeneration and, having at the end of eight to ten days reached a maximum tensile strength for the period, is made up of mature fibroblasts and collagenous fibrils with little if any definite orientation. From then on these slowly over a considerable length of time become oriented parallel to the line of pull of the tendon, taking on grossly and microscopically the appearance of it, so that ultimately the tendon may actually be stronger at the point of repair than elsewhere. A more complicated instance of differentiation and organization is that of the healing of a fracture.[16] The space between the cut ends of the bone is filled with blood, which undergoes the early phases of regeneration as in the severed tendon. Here, however, nearly if not quite concomitant with the appearance of collagen there is a deposit of calcium in the matrix surrounding the cell. This with the proliferating fibroblasts makes up the osteoid tissue which reaches its maximum strength at something over fourteen days, by which time phagocytic cells appear excavating the calcified matrix in part while in other areas the deposition of calcium becomes greater so that organized bone is formed, the structure being eventually oriented in respect to the lines of stress. This process while customarily associated with

fracture, occasionally occurs elsewhere far distant from the supposedly specific and differentiated cells of bone, and may result not only in true bone but also in bone marrow with all its normally diversified cellular elements. This has been reproduced in the experimental animal by the transplant of elements of the wall of the urinary bladder into the rectus sheath, where the same process takes place.[17] Here, apparently the proper environmental field for the conversion of the fibroblastic reaction into bone has been set up and the pluripotentiality of the elemental mesenchymal cell demonstrated, for there are, under these circumstances, no specific differentiated bone cells to be dedifferentiated and then differentiated.

In fact there persists after the completion of the organization and growth of the body certain circumstances in which regeneration is a continuing process. The erythrocyte, for instance, has a limited and known survival time, and new red cells are constantly being formed to replace the older ones. This is likewise the case with the other corpuscular elements of the blood, and the depot where these are constantly regenerated in adult man is for the most part the bone marrow. In early embryonic life the formation of these elements is rather generally distributed but with the further organization of it there is a concentration of this activity to rather limited areas. But the stem cells within these generating areas are very labile and adaptable to demand for any or all of the corpuscular elements of the blood. Under conditions where the turnover of red cells is increased, there is of course increased productivity in the marrow; this occurs rapidly after marked hemorrhage with the appearance of reticulocytes in the blood stream. Even more striking is the plasticity of the progenitors of the leucocytes of the blood. These under normal circumstances are being regenerated at a fairly constant rate for purposes of replacement, but under the stimulus of certain evocators, in a matter of a few hours their formation may be increased manifold. This is most striking in the case of the phagocytic elements and particularly the polymorphonuclear leucocytes. There is, then, in this instance a persisting island of embryonal mesenchyme active throughout the life of the organism, which is pluripotential so far as the corpuscular elements of the blood are concerned. A similar concept obtains with respect to the reticuloendothelial system of Aschoff, which likewise has the constant function of replacement but responds with extraordinary celerity to suitable stimulation in certain infectious diseases such as, notably, typhoid fever. Epithelium, wherever present, provides another instance of regeneration for replacement of wastage, and the germinal layers of the structures which it covers are constantly undergoing cellular division and growth at a sufficient rate to accomplish this. Injury elicits promptly a burst of regenerative activity which tends to restore the normal situation. In the parenchymatous organs there is, likewise, a constant and continuing replacement of the functioning cells, however slow this may be, from persisting embryonal-like cells whose potentiality is that of reproducing the specific cells involved.

It then does not seem unreasonable to presume that there is present throughout the body a residue of embryonal cells, which continue at varying rates to multiply and differentiate as in the embryo, and that in response to injury take on an accelerated activity, which serves for the purposes of repair and is in fact regeneration as understood by the embryologist. The healing of a wound then, as a form of response to injury, involves the reactivation of the normal growth processes which have led to the development of the individual concerned.

SUMMARY

The wound and its repair is an instance, but not a unique one, of "reaction to injury" which may have many inciting causes and various forms of expression. Reaction to injury is a fundamental biologic phenomenon without which neither the individual organism nor the species could continue to exist. The first phase of this reaction is concerned with the removal or neutralization of nonviable material, the second with regeneration.

Both phases are dependent upon the persistence throughout life of primordial or cytoblastic cells of degrees of potentiality which exist in the embryo at various stages of its differentiation. These cytoblasts persist to a varying degree and are active throughout life, even after growth of the organism has ceased. They serve by multiplication and differentiation to replace cells which have become, for whatever reason, nonviable, or to form additional cells for specific growth in response to additional demand. The reaction to injury involves activation of these persisting cells, leading to regeneration and differentiation within the scope of their respective potentialities. The course this takes and the organization of these into structures depend upon the persistence or formation of a suitable "field" of induction.

In general, regenesis follows the pattern of ontogenesis as ontogenesis does that of phylogenesis.

The reaction to injury, and specifically the healing of the wound, is a form of growth that, under normal and uncomplicated circumstances, is primarily autocatalytic and proceeds at a given velocity. This process takes precedence in the body economy, and cannot in so far as is known be materially expedited; it can, however, be delayed or stopped by many complicating factors.

The function of the surgeon is to establish and maintain the optimum conditions for the healing of the wound by avoiding or controlling the factors that may interfere with this normal biologic process.

REFERENCES

1. Cohnheim, Julius, F.: Lectures on General Pathology, in Three Volumes, London, 1889-1890, New Sydenham Society of London.
2. Maximow, Alexander A., and Bloom, William: A Textbook of Histology, ed. 4, Philadelphia, 1942, W. B. Saunders Company, p. 111.
3. Marchand, F.: Der Process der Wundheilung, Stuttgart, 1901, Ferdinand Enke.
4. Spain, Kate C., and Loeb, Leo: Wound Healing, J. Exper. Med. **23**: 107, 1916.
5. (a) Carrel, Alexis, and Hartmann, Alice: Cicatrization of Wounds: The Relation Between the Size of the Wound and the Rate of Cicatrization, J. Exper. Med. **24**: 429, 1916.

(b) DuNoüy, P. LeComte: Cicatrization of Wounds. III. The Relation Between the Age of the Patient, the Area of the Wound and Cicatrization, J. Exper. Med. **24**: 451, 1916.
(c) DuNoüy, P. LeComte: General Equation for Law of Cicatrization of Surface Wounds, J. Exper. Med. **29**: 329, 1919.
(d) Carrel, Alexis: Cicatrization of Wounds; Factors Inhibiting Regeneration, J. Exper. Med. **34**: 425, 1921.
(e) Ebeling, A. H.: Cicatrization of Wounds; Temperature Coefficient, J. Exper. Med. **35**: 657, 1922.

6. (a) Howes, Edward L., Sooy, Joseph W., and Harvey, Samuel C.: The Healing of Wounds as Determined by Their Tensile Strength, J. A. M. A. **92**: 42, 1929.
(b) Harvey, Samuel C.: Velocity of the Growth of Fibroblasts in the Healing Wound, Arch. Surg. **18**: 1227, 1929.
(c) Howes, Edward L., and Harvey, Samuel C.: Recent Studies in Wound Healing, Yale J. Biol. & Med. **2**: 285, 1930.
(d) Harvey, Samuel C., and Howes, Edward L.: The Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, Ann. Surg. **91**: 641, 1930.
(e) Howes, Edward L., and Harvey, Samuel C.: The Age Factor in the Velocity of the Growth of Fibroblasts in the Healing Wound, J. Exper. Med. **55**: 577, 1932.
(f) Howes, Edward L., Briggs, Harry, Shea, Richard, and Harvey, Samuel C.: Effect of Complete and Partial Starvation on the Rate of Fibroplasia in the Healing Wound, Arch. Surg. **27**: 846, 1933.
(g) Harvey, Samuel C.: Reaction to Injury as a Function of Growth, Proc. Inst. Med. Chicago **10**: 70, 1934.
(h) Taffel, Max, and Harvey, Samuel C.: Effect of Absolute and Partial Vitamin C Deficiency on Healing of Wounds, Proc. Soc. Exper. Biol. & Med. **38**: 518, 1939.
(i) Howes, Edward L., Hewitt, C., and Harvey, Samuel C.: Rate of Fibroplasia and Differentiation in the Healing of Cutaneous Wounds in Different Species of Animals, Arch. Surg. **38**: 934, 1939.
(j) Harvey, Samuel C.: The Relationship of Cell Growth, Wound Healing and Food, Medico-Surgical Tributes to Harold Brunn, Berkeley, 1942, University of California Press.

7. Localio, S. A., Casale, W., and Hinton, J. W.: Wound Healing—Experimental and Statistical Study; Historical, Surg., Gynec. & Obst. **77**: 369, 1943.
8. Halsted, William S.: Circular Suture of the Intestine, Surgical Papers **1**: 185, 1928.
9. Fischer, A.: Versuche an Gewebekulturen in Vitro, Virchows Arch. f. path. Anat. **279**: 94, 1930.
10. (a) Wolbach, S. B.: Controlled Formation of Collagen and Reticulum. Study of Source of Intercellular Substance in Recovery From Experimental Scorbutus, Am. J. Path. **9**: 689, 1933.
(b) Lanman, T. H., and Ingalls, T. H.: Vitamin C Deficiency in Wound Healing; Experimental and Clinical Study, Ann. Surg. **105**: 616, 1937.
11. Crandon, J. H., Lund, C. C., and Dill, D. B.: Experimental Human Scurvy, New England J. Med. **223**: 353, 1940.
12. Thompson, D'Arcy W.: On Growth and Form, ed. 2, London, 1942, Cambridge University Press, p. 271.
13. Needham, Joseph: Biochemistry and Morphogenesis, London, 1942, Cambridge University Press, p. 435.
14. Sayad, William Y., and Harvey, Samuel C.: The Regeneration of the Meninges. The Dura Mater, Ann. Surg. **77**: 129, 1923.
15. Mason, M. L.: Rate of Healing of Tendons; Experimental Study of Tensile Strength, Ann. Surg. **113**: 424, 1941.
16. Jones, R. Watson, and Roberts, R. E.: Calcification, Decalcification and Ossification, Brit. J. Surg. **21**: 461, 1934.
17. Huggins, C. B.: The Formation of Bone Under the Influence of Epithelium of the Urinary Tract, Arch. Surg. **22**: 377, 1931.

AN EVALUATION OF MIXTURES OF OSSEIN GELATIN, HYDROLYZED PROTEIN, AND GLUCOSE IN THE PARENTERAL NUTRITION OF POSTOPERATIVE PATIENTS

CECILIA RIEGEL, PH.D., C. E. KOOP, M.D., C. W. SCHWEGMAN, M.D., M. T. BARNES, AND R. P. GRIGGER
PHILADELPHIA, PA.

(From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania)

THE problem of providing an adequate ration for the postoperative patient who cannot take food by mouth is complicated by the fact that most of the nutrient solutions available for this purpose are both too dilute to provide the requisite number of calories in a reasonable volume of fluid and so hypertonic that they produce thrombosis of the recipient vein. One approach to this problem is to use large molecule materials. Only a very limited number of such substances are nonantigenic as well as otherwise suitable for this use. Specially prepared ossein gelatin was developed during World War II as a plasma substitute and proved to be remarkably free from toxic or antigenic properties.[1, 2, 3] While it is one of the few plasma substitutes (as distinct from blood derivatives) with nutritional value, it has long been recognized to be an incomplete protein. Its use in conjunction with a hydrolyzed complete protein was first suggested by Brunschwig and associates.[4] The data which they reported in support of its utilization did not seem to us sufficient to establish the limits of its usefulness, and the following experiments were therefore undertaken.

PROCEDURE

Nitrogen balance studies were completed on twenty surgical patients for five-day periods starting within twenty-four hours following a major abdominal operation such as gastric resection. All patients received approximately 30 calories per kilogram per day and 0.3 Gm. of nitrogen per kilogram per day by vein in 3,000 to 3,500 c.c. of water. No food was given by mouth. Vitamin C and B_1, along with some of the other B vitamins, were generally given parenterally, and the sodium chloride administration was governed by the needs of the individual patient. In group I (ten patients) all of the nitrogen was provided in the form of hydrolyzed casein or hydrolyzed fibrin. In group II (ten patients) 50 per cent of the nitrogen was replaced by the nitrogen of ossein gelatin (Knox P-20). Glucose was added to the solutions to give the desired number of calories. The protein hydrolysate and glucose or protein hydrolysate-gelatin-glucose were mixed in the desired proportions before administration.

The injections were continuous over the twenty-four hour periods and were given from the first to the fifth postoperative days inclusive. Total twenty-four hour urine output was collected for analysis, as well as drainage from the

Received for publication, Dec. 28, 1948.

The ossein gelatin used in this study was provided by the Knox Gelatine Protein Products, Inc., through the courtesy of Doctor Dee Tourtellotte.

stomach obtained by the Wangensteen suction method. Feces were not analyzed, but an average value of 1.0 Gm. of nitrogen per twenty-four hours was added to the total output.[5] Plasma protein concentration, blood volume, and urine total nitrogen were determined as previously described.[6, 7] Gelatin in urine was determined by the method of Seegal and Kendall.[8]

The amount of gelatin excreted in the urine was determined not only during the period of administration of gelatin, but also for three days after the administration was discontinued. This value was added to the amount of gelatin excreted during the period of administration when nitrogen balance was calculated. Four days after administration of gelatin was stopped, the amount of that material appearing in the urine was usually negligible. Patients with a daily nitrogen balance of –0.5 to +0.5 Gm. were considered as being in nitrogen equilibrium, while those below –0.5 Gm. were considered as in negative balance and those above +0.5 as in positive balance.

RESULTS

In Table I are presented nitrogen balances on twenty patients, ten of whom received all their nitrogen as protein hydrolysate, ten of whom received one-half their nitrogen as gelatin, one-half as protein hydrolysate. Of the group receiving protein hydrolysate, two were in equilibrium or in positive balance; eight were in negative balance. The average nitrogen balance calculated for the ten patients is –2.85 Gm. of nitrogen daily. Of the group receiving gelatin plus protein hydrolysate, eight were in equilibrium or in positive balance, and two were in negative balance. The average nitrogen balance for these ten patients is –0.20 Gm. of nitrogen daily. In spite of the fact that an average of 43 per cent of the gelatin injected was apparently excreted unchanged in the urine, the nitrogen balance of patients who received gelatin plus hydrolysate was no lower than in the ten patients who received the hydrolysates of casein or fibrin, presumably complete proteins, as their entire nitrogen intake. Actually, the average nitrogen balance was significantly less negative for the group receiving 50 per cent gelatin nitrogen and 50 per cent protein hydrolysate than in those receiving all the nitrogen as hydrolyzed casein or fibrin.

TABLE I

PATIENTS RECEIVING HYDROLYZED PROTEIN					PATIENTS RECEIVING HYDROLYZED PROTEIN AND GELATIN				
	INTAKE		N BALANCE			INTAKE*		N BALANCE	
NAME	N PER KG. (GM.)	CAL. PER KG.	5 DAYS (GM.)	DAILY AVERAGE (GM.)	NAME	N PER KG. (GM.)	CAL. PER KG.	5 DAYS (GM.)	DAILY AVERAGE (GM.)
To.	0.26	34	-10.6	-2.1	Ku.	0.26	25	+ 4.5	+0.9
Ja.	0.27	31	-11.9	-2.5	Mi.	0.29	29	+12.0	+2.4
Fr.	0.28	32	+ 6.2	+1.2	McC.	0.29	30	+ 5.1	+1.0
Ki.	0.28	39	-21.4	-4.2	St.	0.29	30	+ 2.2	+0.4
Ca.	0.29	28	-28.7	-5.7	Sm.	0.30	29	+16.8	+3.3
Ho.	0.30	30	- 9.0	-1.8	Sto.	0.30	30	-17.5	-3.5
Al.	0.30	30	-11.6	-2.3	Ma.	0.30	31	+ 2.6	+0.5
Du.	0.30	33	-43.7	-8.7	Mar.	0.30	33	-23.2	-4.6
Ah.	0.30	36	+ 0.4	+0.1	Fa.	0.30	33	- 0.7	-0.1†
Go.	0.31	33	-12.7	-2.5	Ta.	0.30	34	- 2.6	-0.5†

*One-half intake, gelatin N; one-half intake, hydrolized protein N.

†Patients whose daily negative balance does not exceed 0.5 Gm. of N considered to be in equilibrium.

Excretion of gelatin in the urine during the five-day period of the test plus the following three days ranged from 25 to 59 per cent of the amount infused with an average of 43 per cent.

None of the ten patients receiving gelatin in this dosage developed any evidence of pulmonary edema though larger doses may produce this complication in elderly individuals, and the possibility of pulmonary edema must be taken into consideration in determining the management of patients with some cardiac handicaps.

DISCUSSION

The results in the ten patients receiving all their food nitrogen in the form of protein hydrolysate were also compared with the results obtained by the enteral feeding of protein hydrolysates reported previously.[7] From the earlier study, eight patients were selected who received by mouth or by a jejunal route amounts of nitrogen in the form of protein hydrolysates and of supplementary carbohydrate which closely approximated the amounts given parenterally in the present study. These data are shown in Table II. The average daily nitrogen balance was +0.35 Gm., which, however, is not significantly different statistically from the average of –2.85 for the intravenous hydrolysate group. This is in consonance with the studies by Madden and his associates[9] which showed that oral feeding of synthetic amino acids (in a patient with ulcerative colitis) was more efficient than the same mixtures given parenterally.

TABLE II

NAME	INTAKE		N BALANCE	
	N PER KG.	CAL. PER KG.	5 DAYS	DAILY AVERAGE
Be.	0.27	26	+13.4	+2.6
Fo.	0.30	31	-12.7	-2.5
SmE.	0.30	32	-21.0	-4.2
Cl.	0.30	33	+ 5.4	+1.0
Cu.	0.30	34	-15.3	-3.0
Ga.	0.30	34	+18.6	+3.7
Ch.	0.30	36	+16.4	+3.2
Ba.	0.30	37	+10.4	+2.0

The finding that the substitution of gelatin (an incomplete protein) as the source of one-half the nitrogen resulted in better rather than poorer nitrogen balance was unexpected. It is the more remarkable in that 43 per cent of the injected gelatin nitrogen was, on the average, recovered in the urine in precipitable form.

Brunschwig, Scott, Corbin, and Moe[4] and Brunschwig, Nichols, and Bigelow[10] have described experiments in which they produced positive nitrogen balance in dogs by intravenous infusion of gelatin and in three human subjects receiving 50 per cent of their nitrogen intake as gelatin intravenously. Brull and Dumont[11] produced positive balance in two human subjects on adding gelatin to their diet.

No explanation for the results obtained has been established. The thought that the gelatin in some way facilitates the use of the hydrolysate has been considered. However, it may be possible that sufficient amounts of gelatin may be

stored in the body to account, at least in part, for the improved nitrogen balance. Studies of the nutritional value of human serum albumin by Gimbel and Riegel,[12] in this department, led to the conclusion that such a mechanism was important.

SUMMARY

Nitrogen balance studies were carried out on two groups of ten patients each, during five-day periods following major operative procedures such as subtotal gastrectomy.

Both groups were given all of their nourishment intravenously, and each patient received approximately 30 calories per kilogram per day and 0.3 Gm. of nitrogen per kilogram per day.

Casein or fibrin hydrolysates provided all of the nitrogen for the first group, and the average daily nitrogen balance was –2.85 Gm.

In the second group, ossein gelatin was substituted for one-half the hydrolysate, and the average daily nitrogen balance was –0.2 Gm.

The first group was also compared with eight similar patients studied previously who received a comparable ration enterally and had an average daily nitrogen balance of +0.35 Gm.

No difference in efficacy was observed between casein hydrolysate and fibrin hydrolysate in this series.

The use of macromolecular gelatin for a part of the nitrogen ration makes possible the use of a solution which is somewhat less hypertonic than is otherwise necessary.

REFERENCES

1. Koop, C. E., Riegel, C., Vars, H. M., Ratcliffe, H. L., Parkins, W. M., and Lockwood, J. S.: Am. J. M. Sc. **205**: 876, 1943.
2. Koop, C. E., Fletcher, A. G., Jr., Riegel, C., and Lockwood, J. S.: SURGERY **15**: 839, 1944.
3. Fletcher, A. G., Jr., Hardy, J. D., Riegel, C., and Koop, C. E.: J. Clin. Investigation **24**: 405, 1945.
4. Brunschwig, A., Scott, V. B., Corbin, N., and Moe, R.: Proc. Soc. Exper. Biol. & Med. **52**: 46, 1943.
5. Reifenstein, E. C., Jr., Albright, F., and Wells, S. L.: J. Clin. Endocrinol. **5**: 367, 1945.
6. Koop, C. E., Riegel, C., Grigger, R. P., and Barnes, M. T.: Surg., Gynec. & Obst. **84**: 1065, 1947.
7. Riegel, C., Koop, C. E., Drew, J., Stevens, L. W., and Rhoads, J. E.: J. Clin. Investigation **26**: 18, 1947.
8. Seegal, D., and Kendall, F. E.: Personal communication.
9. Madden, S. C., Bassett, S. H., Remington, J. H., Martin, F. J. C., Woods, R. R., and Shull, F. W.: Surg., Gynec. & Obst. **82**: 131, 1946.
10. Brunschwig, A., Nichols, S., and Bigelow, R.: Surg., Gynec. & Obst. **82**: 25, 1946.
11. Brull, L., and Dumont, L.: Arch. internat. de physiol. **53**: 17, 1943.
12. Gimbel, N. S., and Riegel, C.: Personal communication.

STUDIES ON BURNS

III. The Effect of Heparin on the Circulating Blood Plasma and Proteins in Experimental Burns

E. Meredith Alrich, M.D., Charlottesville, Va.

(From the Department of Surgery and Gynecology, University of Virginia School of Medicine)

THAT fluid is lost into an injured area and that this loss results in a decreased circulating blood volume have been demonstrated experimentally. In burns correction both of fluid loss into the injured area and of the consequent decrease in blood volume has been attempted by two methods: pressure dressings to limit the amount of fluid lost into the burned area and replacement therapy by infusion of blood and plasma.

In two studies of experimental burns, the observation was made that when the animal is heparinized there is less swelling in the burned area.[1, 2] It was also demonstrated[1] that in nonheparinized animals lymph samples can be collected from a burned area by cannulization of a lymphatic for a period of only six to eight hours, whereas after heparinization lymph samples can be collected for a period of twenty-four hours or longer. On account of these two observations it was postulated that heparin, by preventing the coagulation of the plasma lost into the tissues and thereby allowing it to return to the general circulation by way of the lymphatics, might decrease the amount of edema fluid trapped in the traumatized area. If this tentative explanation is true and there is not an increase in fluid lost externally from the burned area, heparinization should protect the plasma volume and proteins in burned animals. The investigation of this hypothesis is reported here.

METHODS

The standard burn used is one in which there is sufficient fluid and protein lost by the controls to be reflected in changes in the blood volume, hematocrit, and plasma protein of the animal, and which is sufficiently superficial so that no appreciable fluid loss occurs externally through the traumatized surface. By trial and error it was first determined that when the hindquarters of a dog are burned by immersion in water at 75° C. for five seconds, the genitals being protected, there results a reproducible burn which has the characteristics described.

Nembutal anesthesia was employed and was continued until the animals were sacrificed. Twenty-three animals received the standard burn. They were divided into two groups, a control group which included six animals and an experimental group which included seventeen animals. The animals in the control group received no treatment while the animals in the experimental group were given 10 mg. of heparin intravenously immediately following the burn and the same quantity subcutaneously each hour thereafter for

Received for publication, Aug. 18, 1948.

eight hours. This resulted in a marked prolongation of the coagulation time of these animals for the first twelve to eighteen hours after burning. The plasma volume by the Evans-Blue method according to Gregerson,[3] the hematocrit by the use of Wintrobe tubes, and the plasma proteins by the micro-Kjeldahl method were determined on each animal just before burning and at three, six, twelve, twenty-four, and thirty hours following the burn. Animals surviving thirty hours after burning were sacrificed.

RESULTS

All of the animals in the control group survived for the period of observation. In the experimental or heparinized group of animals five died within the first thirty hours following burning, resulting in a mortality rate of 29.4 per cent. The values for one of the control and three of the experimental animals are not included in the results because readings at all of the time intervals were not obtained. Therefore, there are available five animals in the control group and nine animals in the experimental group, for evaluation of the results.

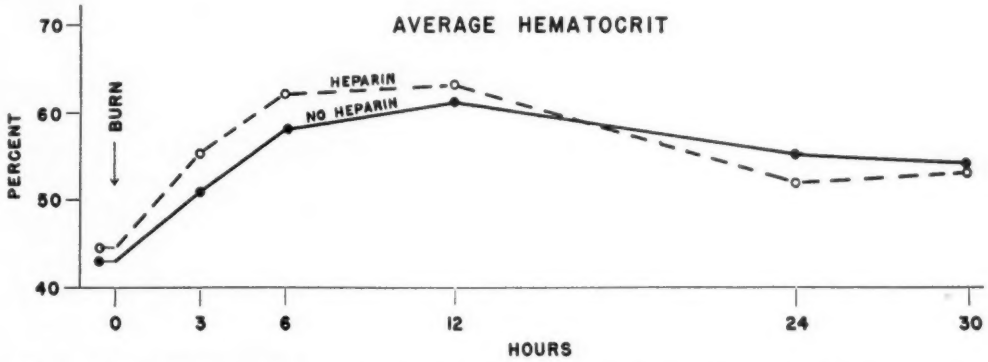


Fig. 1.—Average hematocrit readings following standard burn in five control and nine heparinized dogs.

Average changes in hematocrit in the two groups of animals are shown in Fig. 1. In both groups there is a sharp rise in the average hematocrit value over the first twelve hours of the experiment, followed by a gradual fall during the remaining period of observation, the average hematocrit at the end of the experiment being elevated above the original level. The average hematocrit in the animals which received heparin rose to a slightly higher level and more rapidly than in the control group of animals during the first twelve hours; however, during the period from twelve to thirty hours after burning, the average hematocrit for the heparinized group fell more rapidly than the average for the control group, and at thirty hours it was found to be at a lower level.

The average plasma volume (Fig. 2) decreased rapidly and progressively over the first twelve hours in both groups of animals. The plasma lost in the heparinized group, however, was greater than in the control group during

this period. The average plasma volume in the heparinized group during the period from twelve to thirty hours increased, whereas in the control group it remained essentially unchanged. At the termination of the experiment the animals in the heparinized group had a greater average plasma volume than those in the control group, although at the twelve-hour period the heparinized group had had an appreciably smaller average plasma volume than the control

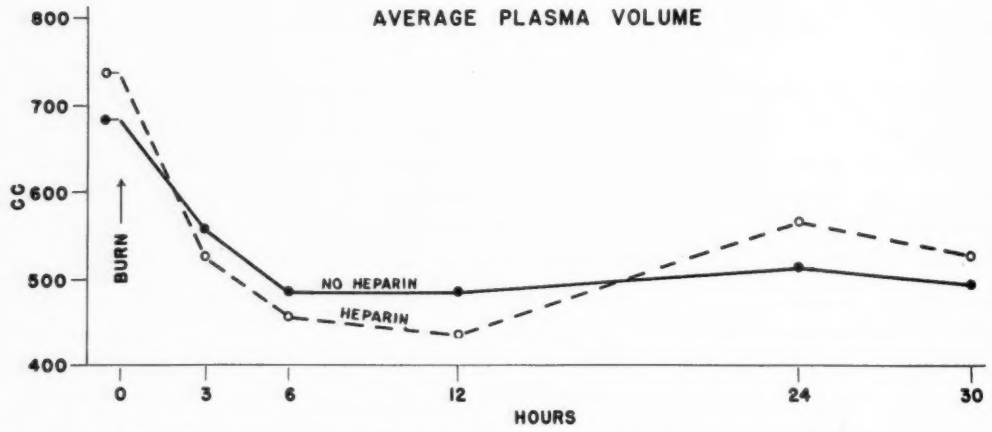


Fig. 2.—Average plasma volumes in some animals as shown in Fig. 1.

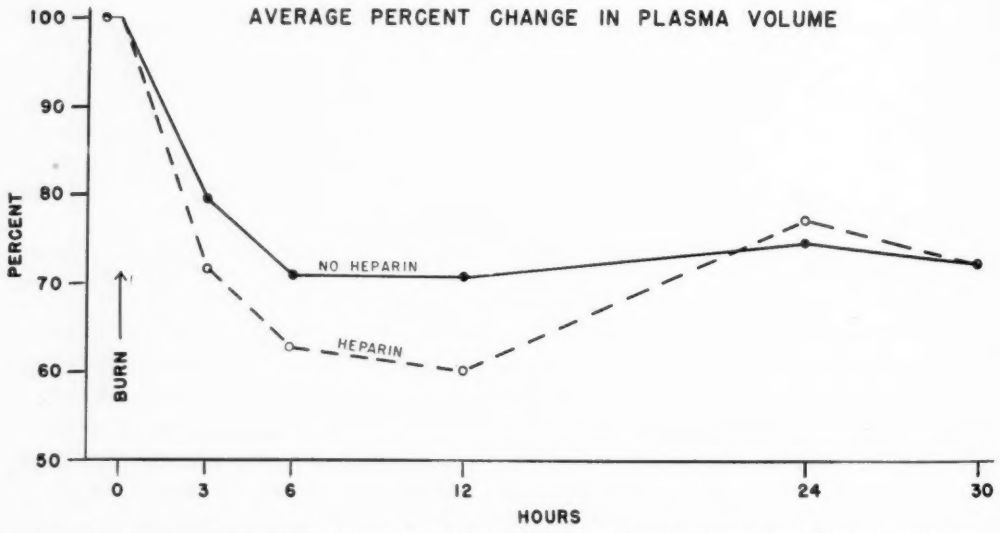


Fig. 3.—Average percentage change in plasma volumes in some animals as shown in Fig. 1.

group. The same result is demonstrated in Fig. 3, in which the average percentage changes in plasma volume from the control level are recorded for the two groups of animals. The average percentage loss is greater in the heparinized group than in the control group during the first twelve hours. The average increase in plasma volume is appreciable in the heparinized group but negligible in the control group between twelve and thirty hours.

Changes in the average total proteins are recorded in Fig. 4 as absolute values for total circulating proteins, calculated from the protein per cent and plasma volume values. The average total circulating protein decreased rapidly in both groups of animals during the first twelve hours, the decrease being slightly greater in the heparinized group. In the period between twelve and thirty hours there was an increase in the average total circulating protein in the heparinized group, whereas there was essentially no change in the control group. The result when expressed as average per cent of change is comparable (Fig. 5).

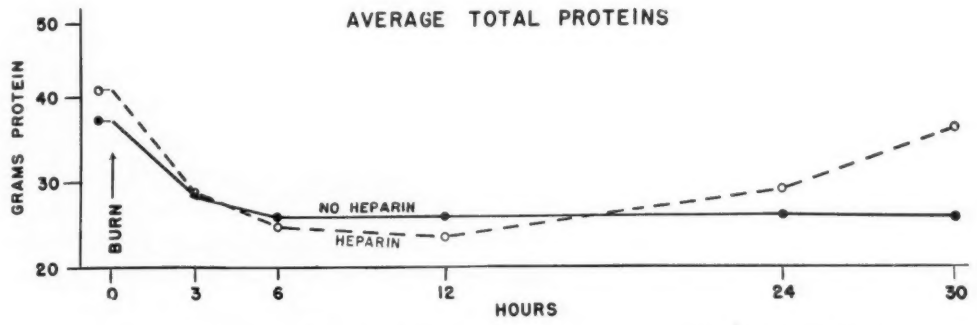


Fig. 4.—Average total circulating proteins in same animals as shown in Fig. 1.

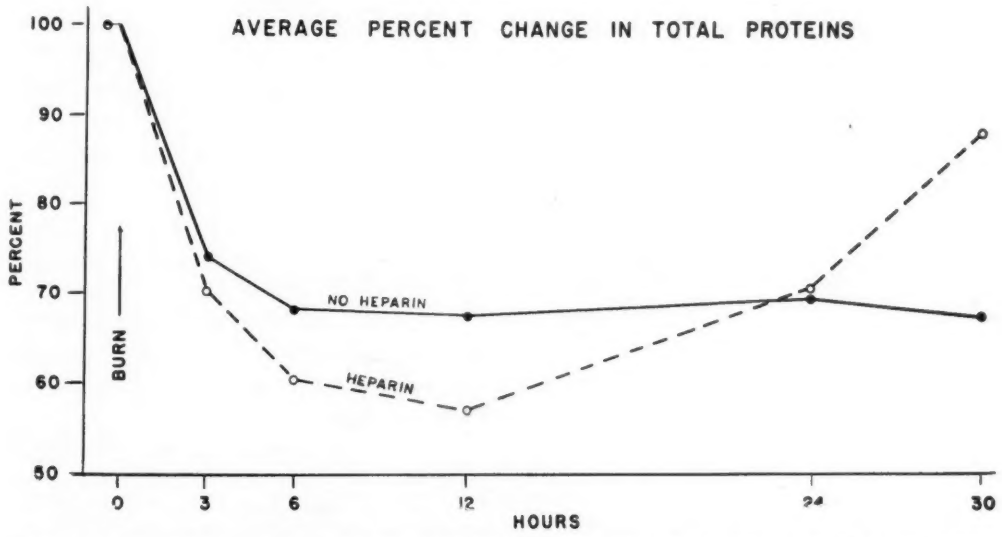


Fig. 5.—Average percentage change in total circulating proteins in same animals as shown in Fig. 1.

DISCUSSION

Heparinization following burning apparently results in a greater loss in plasma volume during the first twelve hours after burning as compared with control nonheparinized animals. This was demonstrated in the present study by the greater decrease in plasma volume and in total plasma proteins and

the greater rise in hematocrit in the heparinized groups of animals during this period. The reverse is found to be true during the period from twelve to thirty hours following burning. There was a greater increase in plasma volume and total proteins, and a greater fall in the hematocrit value in the heparinized series. This was sufficient in the heparinized group to result in the average hematocrit being below and the average plasma volume and total proteins above those of the control group at thirty hours. During the interval between twelve and thirty hours, an appreciably greater amount of plasma and protein is apparently returned to the circulating blood in the heparinized group of animals than in the control, presumably by way of the lymphatics. Both the early greater loss of plasma and the more effective recovery may be explained by the absence of coagulation of the exudate in the tissues and lymphatics resulting from heparinization. Whether this hypothesis is the explanation of the mechanism has not been determined by sections of the traumatized area to demonstrate a difference in fibrin content by special staining techniques. It has also not been determined whether this apparent difference in exchange of plasma and proteins between the damaged area and the general circulation in the two groups of animals would influence the healing of the traumatized areas.* The effect on healing would be interesting to compare with the differences which have been demonstrated experimentally and clinically to exist in cases of frostbite.[4]

The higher mortality from the burns in the heparinized group has not been fully explained but may in some instances be correlated with a sharp drop in plasma volume and hence a deep level of shock. However, at least two of the five animals that died had an additional cause of shock in widespread hemorrhage obviously due to an overdose of the drug.

The higher mortality in the heparinized animals obviously precludes the use of heparin in the management of clinical burns.

CONCLUSIONS

Heparinization following a standard burn in dogs results in (1) an appreciable mortality, (2) a greater loss in plasma protein and plasma volume during the first twelve hours following burning, and (3) a greater return of lost plasma and proteins to the general circulation from twelve to thirty hours after burning than in control animals with a comparable burn.

REFERENCES

1. Alrich, E. M.: Studies on Burns, II. Observations on a Vasoconstrictor Substance in Lymph From a Burned Area, SURGERY **15:** 908-912, 1944.
2. Glenn, W. W. L., Peterson, D. K., Drinker, C. K.: Flow of Lymph From Burned Tissue, With Particular Reference to the Effects of Fibrin Formation Upon Lymph Drainage and Composition, SURGERY **12:** 685-693, 1942.
3. Gregerson, M. I.: A Practical Method for the Determination of Blood Volume With the Dye T-1824, J. Lab. & Clin. Med. **29:** 1266, 1944.
4. Lange, K., and Leowe, L.: Subcutaneous Heparin in the Pitkin Menstruum for Experimental Human Frostbite, Surg., Gynec. & Obst. **82:** 256-260, 1946.

*Studies to determine whether or not healing of burns is affected by heparinization are in progress.

A STUDY OF VEHICLES AND ADJUVANTS FOR THE SULFONAMIDES AND PENICILLIN

EDWIN J. PULASKI, M.D., FORT SAM HOUSTON, TEXAS

HISTORICAL NOTE[29, 41]

CHEMOTHERAPY is not a modern medical development. A study of old Egyptian papyri indicates that infections occurred following accidents and battle injuries in ancient times, just as they occur today, and that they were treated by chemical means. The prescriptions used in their treatment antedate these records and seem to have been handed down through many generations of Egyptian physicians. Similarly, all through medical literature, before as well as after Hippocrates, are records of the external and internal use of chemicals in the treatment of infections.

The rationale of the application of antiseptics to wounds was not appreciated, in spite of the general use of these agents, until the discoveries of Pasteur in 1863 brought about the realization of the bacterial etiology of wound infections and until the surgical significance of this realization was pointed out by Lister in 1867. Even earlier, Oliver Wendell Holmes and Ignaz Semmelweis had concluded that puerperal fever could be prevented by the precautions now included under the term asepsis, but modern surgical procedures are based on Lister's observations that if access of bacteria from without is rigidly prevented, wound suppuration will not occur.

Lister achieved the elimination of infection in compound fractures by the application of crude carbolic acid. This heroic method, however, was not always successful, and was frequently harmful, so harmful, in fact, that the author of the method later deprecated bringing this corrosive substance into contact with tissues of the human body. The potential efficacy of antiseptic or disinfectant substances, on the other hand, has been appreciated since his initial discovery, and the search for an ideal antiseptic has gone on over the years.

A promising lead was opened up in 1876 when Weigert found that certain stains or dyes were taken up by microorganisms, which were thus made clearly visible under the microscope. Koch, von Behring, and others had been unsuccessful in their attempts to find chemicals which were effective as internal disinfectants against bacterial diseases and had come to the conclusion that failure was inevitable because the tissues and organs of the body would be more susceptible to these agents than would the organisms they were designed to kill. Ehrlich, however, refused to accept this council of despair and vigorously pursued his search for chemicals which would have a selective action on

Submitted in partial fulfillment of the requirements for the degree of Doctor of Medical Science in the Faculty of Medicine, Columbia University, New York, N. Y.

Now Major, Medical Corps, United States Army, Chief of the Surgical Research Unit, Brooke General Hospital, Brooke Army Medical Center, Fort Sam Houston.

Received for publication, Aug. 6, 1948.

bacteria and which at the same time would be relatively nontoxic to the host. In this search he was ably seconded by Hata. It is of interest, in 1948, to remember that the medical profession is chiefly indebted to a Japanese and a German for the basic discoveries of modern chemotherapy and that Ehrlich said in 1913, at the International Congress of Medicine, that in the world of science all national barriers had disappeared.

The lead offered by earlier workers with dyes was eagerly pursued in many countries. It was found that these agents had a selective action on bacteria, being potent against some microorganisms and inert against others. Furthermore, by the addition or withdrawal of radicals of various kinds it was found that the potency of various dyes could be increased, while their toxic effects on the tissues of the host could be decreased. One group of dyes, the acridines, seemed particularly promising. Ehrlich demonstrated that acriflavine has a powerful lethal action on trypanosomes, and Neufeld found it effective against the pneumococcus and the chicken cholera bacillus.

In England, Browning became one of the chief advocates of dye therapy, particularly for topical application in wound infections and for prophylaxis against infection in accidental wounds and battle casualties. Fleming, on the other hand, warned against their use, on the basis of his own observations concerning their deleterious action on leucocytes and tissue cells.

From these and other studies there gradually emerged three dyes, acriflavine, gentian violet, and mercurochrome, which were given extensive clinical trials, particularly in the treatment of infections caused by *Streptococcus hemolyticus* and Staphylococcus. Hundreds of cases were treated by one or another of these dyes, by both systemic and topical application, and many favorable reports appeared in the surgical literature. Along with the favorable reports, however, appeared reports of poor results, ineffectiveness, toxic reactions, and fatalities undoubtedly caused by their use.

As these unfavorable reports began to accumulate, the dyes gradually fell into disrepute, and a decade of antiseptic nihilism followed. As late as 1936, at a meeting of the American College of Surgeons, the preponderance of opinion was that chemical agents were of no avail in either the prophylaxis or the treatment of surgical infections, no matter how they were applied.

At this meeting, however, an occasional voice was raised to suggest that such pessimism was not warranted because of the promise of the new dye of the azo series, Prontosil, which had recently been advocated by Domagk[8] and by Colebrook.[5] During the decade of reaction against antiseptic agents, the search for a more effective and less harmful dye had continued in a few laboratories and was rewarded in 1935 when Domagk reported his experiences with Prontosil. His experiments with mice had shown that this dye, when given by mouth, was effective against massive injections of hemolytic streptococci into the peritoneal cavity. His experimental results, which were confirmed by Levaditi and Vaisman[22] and by Nitti and Bovet,[32] were put to early clinical trial by Colebrook and Kenny,[6] who had the unusual opportunity of treating large numbers of patients with puerperal fever caused by the

hemolytic streptococcus in Queen Charlotte's Hospital, an institution designated to receive such cases from all parts of London. As their experience accumulated, it promptly became evident that the use of this new agent not only reduced the mortality of puerperal fever but also minimized the intraperitoneal spread of the infection and shortened the duration of illness in the patients who survived.

In the meantime, it had been demonstrated by several French workers that the active element in Prontosil is the colorless fraction sulfanilamide, a far simpler compound. The clinical effectiveness of sulfanilamide was also confirmed by Colebrook and Kenny.

Colebrook and Kenny's clinical results were supported by laboratory studies[7] to the effect that the blood of man and of animals treated with Prontosil or sulfanilamide is more bacteriostatic than the blood of normal persons but that it is not bactericidal except for extremely small inocula. Much the same observations were made when sulfanilamide was added to the blood in vitro. It was correctly concluded from these observations that Prontosil breaks down to the active sulfanilamide and that the role of the drug in therapeusis is to interfere with the multiplication of organisms within the body but that it does not destroy them.

During the next two or three years the use of sulfanilamide, which was cheap and readily obtainable, first became widespread and then became promiscuous. It was used for all types of infections and was often used before an infection was diagnosed or the causative organism found. Only in those institutions in which it was possible to determine the nature of the etiologic agent could anything definite be learned concerning the limitations of the sulfonamides in surgical infections.

The comparative chemical simplicity of the sulfonamides and the feasibility of their synthesis permitted the preparation of many derivatives of the original sulfanilamide. By 1942 sulfathiazole, sulfadiazine, and sulfapyridine, as well as other sulfonamides, had been developed and made available commercially, and their efficacy in the therapy of pneumococcic, meningococcic, gonococcic, *Shigella dysenteriae* and *Escherichia coli* infections had been firmly established.[38] So great was the enthusiasm for them, in fact, that the feeling became fairly general that all infectious disease could be combated by these wonder drugs, a feeling that was enhanced by successive announcements of the discovery of new sulfonamides of apparently increased potency and apparently lower toxicity.

Penicillin, a solid substance extracted from broth cultures of the mold *Penicillium notatum,* was discovered by Fleming[10] in 1929 but did not become clinically important until 1943, after it began to be produced in quantity.[12] It proved more effective than the sulfa drugs in its action against nearly all gram-positive organisms and had the additional advantage of extremely low toxicity. Moreover, when it is applied locally, it is not inhibited by large numbers of bacteria or by the presence of blood, pus, peptones, or necrotic tissue.

When it is applied topically it tends to diminish exudate rather than increase it. Drug-fastness less frequently occurs with penicillin than with the sulfonamides. The instability, which was initially a disadvantage, has been largely overcome. Penicillin, however, possesses specificity of action, is destroyed by certain penicillinase producing microorganisms, and is rapidly absorbed and excreted, so that knowledge of the bacteriology of the infection and methods of administration are matters of considerable importance in connection with its use.

It is a somewhat paradoxical fact that these various discoveries, in spite of their enormous importance, somewhat confused the whole subject of antisepsis and disinfection. These are not simple matters, and advances in knowledge of the basic facts governing the action of antiseptics, together with changing concepts in the approach toward achieving disinfection or sterilization of wounds, have added immeasurably to their complexity. Furthermore, the enormous literature which has accumulated on many aspects of the problem has not always been helpful.

For these reasons, it is necessary to preface this presentation with a statement of certain fundamental principles, including (1) the mode of action of antiseptics, (2) the need for such agents in surgery, and (3) a review of the agents available for producing sterility by physical means and by antiseptic or disinfectant methods prior to the introduction of these new agents.[2, 11, 23, 34]

DEFINITIONS

Sterility, which implies that an object (the term being used to include wounds) contains no living bacteria, protozoa, or fungi, is the ideal surgical state. Although the terms sterilization and disinfection are frequently used as synonyms, disinfection implies, as sterilization does not, that chemicals (that is, disinfectants or antiseptics) have been employed to destroy microorganisms.

The term disinfectant is ordinarily reserved for agents used to destroy microorganisms in inanimate objects or on the intact skin since most of them are so constituted that in addition to destroying microorganisms they are also destructive or harmful to the human tissues.* Antiseptics are substances which sometimes kill bacteria and sometimes simply prevent their multiplication, the mode of action being determined both by the character of the agent and by its method of use (that is, its concentration).

The term chemotherapy, which was coined by Ehrlich, is today accepted to mean treatment by means of an antiseptic substance which inflicts maximal injury on the bacteria while at the same time it does no harm or minimal harm to the tissues of the body. Antibiotic therapy implies the treatment of infectious disease by substances elaborated by microorganisms.

*While disinfection by physical means is not a part of this discussion, it should be mentioned, for the sake of completeness, that sterilization can be accomplished by the use of (1) dry heat or hot air, (2) moist heat, and (3) ultraviolet light. The latter method does not effect complete sterilization but brings about a reduction in the total number of bacteria present. It must be used with caution because of the possible effects on the eyes and the skin. Both dry and moist heat, if properly employed, can achieve complete sterilization, though the mechanism of destruction of bacteria is entirely different. Electronic methods are not yet fully developed, but promise much for the future.

PROPERTIES OF THE IDEAL ANTISEPTIC AGENT

The ideal antibacterial agent would be one which was powerfully germicidal against all pathogenic bacteria in the bodily environment in which its action was required but which would, at the same time, be completely inactive against the tissues of the body. Such an agent, it may be said categorically, does not exist at this time. Other characteristics which would be highly desirable include the following:

1. *Physical properties.* The antiseptic substance should be available in a form permitting rapid delivery and easy access to the area needed. This means that it must be soluble in tissue fluids well beyond effective levels and must be capable of penetrating beyond tissue exudates to the site of proliferation of the offending organisms. It also means that the vehicle in which it is incorporated for application must be inert but must release the substance in effective concentrations on contact with tissues.

2. *Stability.* The antiseptic substance should be stable on exposure to light, air, and changes of temperature and humidity. It must also be capable of being transported without decomposition.

3. *Low toxicity.* The antiseptic substance should lack any tendency to irritate tissues when it is applied locally or to cause any adverse reaction when it is administered systemically.

4. *Elimination.* The antiseptic agent should be easily removed from wounds or from dressings when it is used locally.

5. *Low cost.* The antiseptic substance should be comparatively easy to prepare and the cost both of the constituents and of the process of preparation should be low enough to make it generally available.

MODE OF ACTION OF ANTIBACTERIAL AGENTS

The proper selection of antibacterial agents suitable for the various exigencies of surgical practice requires an understanding of their physical and biologic as well as their chemical properties.

Duration of Exposure to Antiseptic Agents.—The duration of exposure of the organisms responsible for a given infection to the antiseptic agent used to control them is intimately related to the concentration of the agent. It is an established fact that if concentration is increased, less time is required for germicidal action by an effective agent. There is, however, a considerable variation in the speed of action of the various antiseptics. The hypochlorites and peroxide of hydrogen, for instance, act quite rapidly as compared with the heavy metals and even more rapidly as compared with the sulfonamides, which act quite slowly.

Temperature of Antiseptic Agents.—The temperature at which an antiseptic or disinfectant is employed plays a part in its efficiency. A high temperature increases germicidal potency, particularly when the phenols are used. This is, however, chiefly a theoretical consideration. From the practical standpoint the use of an antiseptic at high temperatures is not feasible in vivo. The solution would either burn the tissues or would rapidly assume the temperature of the body.

Mode of Application.—The mode of application of the antiseptic is related to both concentration and duration of exposure. A mouthwash, for instance, which remains in contact with the tissues for only a brief time, must be of such concentration and efficacy as to kill bacteria promptly. An ointment, on the other hand, which remains in contact with the tissues for a considerable period of time, theoretically may be of lower concentration. The antiseptic action of ointments is, however, frequently limited to the prevention of multiplication of bacteria.

The choice of the mode of application of an antiseptic agent introduces two other problems: (1) how it can be applied to an area so as to exert maximum effects, and (2) how it can be maintained in the area long enough to achieve the desired results. Both of these problems have to do with the vehicle in which the antiseptic is applied. Aqueous solutions usually provide maximum antibacterial action but drying is slow, which lessens their usefulness in the preparation of the skin for operation. When alcohol is used as the vehicle, evaporation is rapid and drying correspondingly rapid, but otherwise alcohol has few advantages over water. Generally speaking, any vehicle other than water causes some loss of antiseptic power, though this loss may be deliberately assumed because the vehicle employed results in greater solubility, reduces toxicity, or facilitates application.

Phenol is an illustration of how important the vehicle of application may be. Aqueous solutions containing 5 per cent of phenol are highly toxic to tissues and are not impractical for clinical use. The same concentration in petrolatum, on the other hand, is bland and nonirritating to wounds. The use of petrolatum, however, does not solve the problem: Because phenol has a greater affinity for petrolatum than it has for water it is released so poorly from the base that the ointment, for all practical purposes, is inert.

Experience has shown that for immediate, rapid effects, an aqueous isotonic solution is preferable. When more prolonged action is desired, a carbowax water-soluble base, a vanishing cream base, or a lanolin type base is satisfactory.* Since antiseptics are released from these bases slowly, higher concentrations must be used than would be necessary if aqueous solutions were used. Comparative data are needed for the quantitative expression of the rate of release of antiseptics from various vehicles in comparison with their rate of release from water.[13, 21]

Potency of Antiseptic Agents.—The potency of an antiseptic is usually expressed in terms of its phenol coefficient. This coefficient is obtained by dividing the maximum inhibitory dilution of the unknown agent by that of phenol, the inhibitory dilution of which is well known. Information as to the minimum concentration in which an antiseptic will act in vitro is of value in that it serves as a guide for the selection of the concentration to be used in wounds. If

*Carbowax, which is the trademark of Carbide and Carbon Chemicals Company, products, is a mixture of polyglycols. An excellent base may be prepared by using 45 parts of carbowax (4,000) and 55 parts of propylene glycol. A vanishing cream base recommended by Jenkins[17] is made by using oil phase petrolatum, 48 ml., Arlacel C, 2 ml., aqueous phase-tween 80, 0.25 ml., and water to make up 50 ml. Arlacel C and tween 80 are available commercially. An excellent lanolin type base can be obtained commercially.

a concentration greater than this minimum is tolerated by the tissues, the antiseptic is likely to be successful.

Influence of Body Fluids on Potency.—The situation is not quite as simple, however, as this statement might imply. Antiseptics almost invariably are of greater effectiveness in vitro than in vivo. The presence of body fluids and tissues decidedly alters the picture, the alteration varying according to the antiseptic employed. Thus, phenolic compounds are greatly affected in their germicidal activity by dilution, while the mercurials and the dyes are only gradually reduced in activity by progressive dilution. The organic matter with which the antiseptic comes into contact when it is used in vivo consists of plasma proteins, blood cells, and foreign bodies, such as sequestra and necrotic tissue. These interfere in varying degrees with antibacterial action. It is, therefore, highly important to know how a given antiseptic behaves in the preesnce of such material and whether after contact with them it retains any appreciable antibacterial effect.

Specificity of Antiseptic Agents.—The bacterial species present in a given case chiefly determines the efficiency of the antiseptic agents used to control them. All species are not equally susceptible to antiseptics. Spore-formers and tubercle bacilli are quite resistant to all antiseptics because of their impenetrability. Gonococci and meningococci are rather easily killed, but *Streptococcus faecalis, Pseudomonas aeruginosa,* and other gram-negative organisms possess considerable refractoriness to numerous antiseptics.

Selectivity of Antiseptic Agents.—Furthermore, many antibacterial agents show striking degrees of selectivity in their effect on bacteria. Penicillin and gentian violet, for instance, are strongly inhibitory to staphylococci but are only slightly active against most gram-negative organisms. Acetic acid in a concentration which would scarcely affect most organisms readily destroys *Pseudomonas aeruginosa,* an organism which is highly resistant to most substances. Obviously, a knowledge of their selective action is imperative in the proper choice of the antibacterial agents to be used against specific organisms.

Drug Resistance.[36]—Microorganisms which are not originally resistant to certain antiseptics or which are originally susceptible to them may become resistant to them if they are improperly used. It is a well-established fact that exposure of bacteria to sublethal doses of an antibacterial agent often results in the propagation of resistant and mutant forms which become increasingly difficult to kill. This fact has extremely important therapeutic implications. It implies the necessity for adequate concentrations in the early stages of treatment of an infection, as well as the prompt substitution of one agent for another if habituation of the organism is suspected.

Tissue Toxicity.—All known antibacterial agents are toxic in some degree to the tissues as well as to bacteria, but the toxicity of the various agents for tissues is widely different. A number of methods have been devised for testing the tissue toxicity of those agents whose low toxicity warrants their further investigation and continued clinical use after lethal tissue poisons have been

screened out. Minimal lethal doses can be determined by intravenous, subcutaneous, and intraperitoneal animal injection, information which is essential for drugs which are administered systemically. The effect on delicate tissues and on mucous surfaces can be determined by the application of the agent in question to the conjunctiva of rabbits.

When the antiseptic is to be used topically, the effects on the skin, muscles, connective tissue, and blood cells are of primary significance. The cells of tissues exposed to antiseptics can be studied histologically in experimental wounds or by tissue culture. The effect of antiseptics on leucocytes can be determined by direct study of the blood cells. The relative vulnerability of fibroblasts in tissues is unknown, and it is not established that the behavior of one type of cell can be assumed to be similar to that of another type.

An ingenious test has been devised by Howes[16] to determine the effect of the application of antiseptics on wound healing. The antiseptic to be tested is applied to wounds produced in the ears of rabbits, and serial photographs are taken to establish the rate of epithelization in terms of change in the perimeter of an island of epithelium in the center of the wound and the effect of the antiseptic on the growth of the surrounding granulation tissue. Data supplied by such tests as this offer the only possible method for the accurate evaluation of the relative toxicity of various antiseptics which do not produce immediate and gross toxic effects.

Evaluation of Antiseptic Agents.—As already stated, an ideal antibacterial agent has not yet been perfected. Many compounds are antiseptic in vitro, but no single one possesses all the specific functions or properties which would make it ideal. One, for instance, may be outstanding in speed of action but may lack the outstanding penetrating power which another, lacking in outstanding speed of action, may possess.

A multitude of tests is therefore necessary for the evaluation of every antiseptic, and the results secured by these tests must be evaluated with equal care. The following points, at least, must be determined: (1) the proper concentration, (2) the maintenance of the desirable concentration, (3) the period of time during which exposure of the antiseptic to the wound must be maintained, (4) the changes produced by the antiseptic in the bacterial flora of the wound, (5) the effect of the antiseptic on tissue repair, (6) the degree of inhibition of the antiseptic by its contact with organic matter, (7) the possibility of the production of drug resistance.

Esthetic considerations, such as staining, color, and odor, are perhaps less important than these considerations, but they cannot be disregarded. The coloration inevitable in the use of dyes, for instance, makes these compounds unpopular.

Data on all of the points listed are often not available for all antiseptics. Commercial manufacturers, by stressing one point of superiority or another, have popularized a large number of antiseptics, some of which are undoubtedly superior to others. Clinical therapeutic tests unquestionably provide the best criteria for the selection of effective agents if they are complete and if the number of cases is significant. Meleney's warning[27] as to the many variables

which make up any group of "like" surgical cases must, however, be borne in mind.

INDICATIONS FOR THE USE OF ANTISEPTIC AGENTS IN SURGERY

All surgical procedures are carried out under what may be termed nonideal circumstances. To the risk of the bacteria which are normally present on the skin and in certain cavities of the body are added the risk of the bacteria which are present in infectious states and the risk of the implantation of other bacteria as part of the trauma of surgery or for other cases. Disinfection and antisepsis are, therefore, required to prevent the implantation of bacteria or, if infection is already present or should occur, to minimize its damaging consequences. In general, the following antiseptic (or sterilizing) precautions should be taken:

1. Air in operating rooms should be sterilized and cross-infection should be eliminated in wards.

2. Sutures, tubes, drains, powders, solutions, knives, scissors and other instruments, needles, linens, and any other object which comes in contact with the patient's wound should be sterilized.

3. Contamination of gloves or hands by contact with infected material on dressings or from other sources should be avoided when possible and cared for by disinfecting methods when it has occurred.

4. The microorganisms on the hands and arms of the surgeon and his assistants and on the skin of the patient should be eliminated before operation is undertaken.

5. Preoperative preparation of the oral cavity should be a part of the preoperative routine when oral sepsis is present, to minimize the risk of respiratory complications after inhalation anesthesia.

6. Microorganisms in the gastrointestinal tract should be destroyed or inhibited, so that abdominal operations will be attended with less risk of infection.

7. Infections of the lungs and the urinary tract are preferably prevented; they must be controlled if they develop incident to or following surgery.

8. Accidentally produced wounds are all contaminated and are therefore potentially infected.[3, 33] They are frequently incurred under circumstances in which ideal surgery is impossible because of such considerations as time, geographic location, or the anatomic nature of the wound. This is particularly true in time of war, when the need for antiseptics is increased as adjuvants to such fundamental surgical procedures as débridement, control of hemorrhage, and drainage.

9. Wounds in which microorganisms have already gained a foothold and are producing an inflammatory process require appropriate treatment with antiseptics, and often require surgery as well.

10. Methods for the destruction or inhibition of organisms which have traveled from a portal of entry by the blood or lymphatic systemic system to other parts of the body, producing a generalized infection, should be instituted at once.

THE DEVELOPMENT OF MODERN CHEMOTHERAPY

Prior to the introduction of the sulfonamides in 1935 antiseptic agents had, with very few exceptions, acted primarily by chemical activity on protein. These so-called surface antiseptics included (1) acids and alkalies; (2) alcohols; (3) aldehydes; (4) anionic and cationic types of antiseptics; (5) the dyes and organic bases, including azo dyes, acridines, fluorescein dyes, basic dyes, and methylene blue; (6) quaternary ammonium compounds; (7) halogens; (8) heavy metal salts and compounds; (9) oxidizing agents; and (10) phenols and phenolic derivatives.

These categories of surface antiseptics, each of which contains numerous agents, illustrate the efforts which have been made through the years to improve surgical antisepsis and develop an all-purpose antiseptic. The effort has failed, as perhaps might have been expected, and has given rise to two substitute schools of thought. The first school illustrates the trend which might be termed antiseptic nihilism. It depreciates the use of any antiseptic in wounds and substitutes for them the use of agents to stimulate the normal mechanisms of the body to combat infective processes. Advocates of this policy would use only heat and isotonic (passive) or hypertonic (active) salt solutions (lymphagogues) such as sodium chloride, sodium sulfate, and magnesium sulfate.

The second trend is far more rational. It substitutes for the all-purpose antiseptic the choice of specific agents for specific requirements. It selects the agent which will overcome or control the bacteria present in the most effective manner, with minimal expense to surrounding tissue. This trend is in essence, the concept of chemotherapy.

The outbreak of World War II in Europe in 1939 coincided with the time at which the sulfonamides were coming into general use. It was immediately evident that they had a remarkably potent action in battle wounds. Deaths from sepsis were almost eliminated. The application of sulfa powders to fresh wounds enjoyed a wide popularity and, in the opinion of many observers, promised to supply the final answer to the problem of disinfection of traumatic wounds.

Scientific data to substantiate these impressions were, however, lacking. The reverses suffered by the Allies in the early phases of the war, culminating in the retreat to Dunkirk, resulted in the loss of practically all records concerning the actual effects of local sulfonamide therapy. Furthermore, the necessarily rapid transfer of patients from one installation to another interrupted follow-up studies and made impossible the observation by the same observers of a series of wounds from the time of wounding to complete wound healing. As a result, conflicting opinions developed regarding the actual effect of the sulfonamides in the elimination of local infection. There was general agreement, on the other hand, that the parenteral administration of these agents effectively controlled spreading infection and septicemia caused by microorganisms susceptible to their action.

In 1942 the Committee on Surgical Infections, Division of Medical Sciences, National Research Council, Office of Scientific Research and Development, organized and put into operation in nine different cities of the United States a coordinated study for the purpose of appraising the real effects of the sulfonamides in the prophylaxis and treatment of infection in traumatic wounds and burns. When the study had proceeded for about eighteen months, and when the results of 1,500 traumatic wounds and burns had been tabulated and analyzed,[26] it became quite evident that sulfonamide therapy not only was not the answer to the management of all surgical infections but that it actually left much to be desired, for the following reasons:

1. The presence in wounds of devitalized tissue, pus, and other substances capable of antagonizing these agents was found to inactivate the sulfonamides in varying degrees, with the result that concentrations achieved by either systemic administration or by local application by dusting were inadequate to meet the problem of preventing or controlling local infection.

2. Sulfathiazole and sulfadiazine, as well as other sulfa drugs, were found to have a low degree of activity against *Staphylococcus aureus*, which is the most ubiquitous organism inhabiting open wounds.

3. Soluble sulfonamides, such as sulfanilamide or sodium sulfadiazine, while more effective, because of the large concentrations possible, were either rapidly washed into the dressings by exudation or were rapidly absorbed into the circulation. The use of excessive amounts of these solutions, moreover, on large denuded areas such as burns, carried with it the risk of toxic blood levels and crystallization with blockage in the urinary tract.

4. The topical use of the more insoluble compounds, such as sulfathiazole and sulfadiazine, was demonstrated to cause wound irritation, increased exudation, delay in wound healing, and excessive scar formation.

5. Contact of the sulfonamides with the intact skin for as little as five days not infrequently brought on troublesome and dangerous sensitization reactions, which made subsequent parenteral therapy impossible or difficult.

6. Sulfonamide compounds were shown to be incapable of penetrating and sterilizing organized blood clots and devitalized tissue.

Progress in the development and clinical application of penicillin made it clear that this agent, like the sulfonamides, was effective in the control and treatment of spreading types of infection. On the other hand, local sepsis, whether it originated in wounds or in burns, did not seem to have been challenged to nearly the same degree by either class of bacteriostatics. Both types of agents, in addition, were impotent against, or were inactivated by, gram-negative bacteria.

A further, and major, difficulty attending the use of the sulfonamides and penicillin was the lack of a vehicle which would act as a depot for whichever was used, so that, on its application to the wound, sufficient amounts of the bacteriostatic agent would be released over a sufficiently long period of time to destroy the growth of all microorganisms.

OBJECTIVES OF STUDY

The purpose of this study was therefore twofold: (1) to search for a vehicle which would hold the sulfonamides and other bacteriostatic agents in wounds in higher concentrations and over longer periods of time than was possible by the means presently available, and (2) to search for and examine other chemical agents showing activity against gram-negative bacteria. A clinical evaluation of presently available agents was part of the latter phase of the study.

Attention was focused on the search for an antibacterial agent (or agents) effective against gram-negative organisms for these reasons:

1. Sulfonamides are limited in their activity against certain gram-negative bacteria also capable of elaborating para-aminobenzoic acid during growth, which is the antagonist of the sulfonamides.[20]

2. Gram-negative bacilli release in liquid media phospholipids[9] which nullify in mixed cultures the antibacterial effects of such bacteriostatic agents as tyrothyricin and the large class of cationic detergent antiseptics such as Zephiran.

3. Many gram-negative rods commonly found in mixed cultures produce an enzyme (penicillinase)[1] which destroys the growth-inhibiting properties of penicillin. Penicillin, when used locally, had proved to be an effective bacteriostatic agent, and it therefore seemed that the most urgent need in the treatment of wound infections was for an agent which would be effective against gram-negative pathogenic bacteria.

4. Gram-negative organisms produce an abundant purulent exudate which, because pus may rapidly escape through dressings onto bedclothes, utensils, and hands, greatly increases the risk of cross-infection in hospital wards. The rapidity with which gram-negative organisms grow in cultures may result in masking the presence of other organisms actually causal of the (mixed) infection.

The need was clear for a substance which would be effective in vitro against surgically important gram-negative rods and which would retain its activity in wounds without causing local or general untoward effects. Other desirable properties of this hypothetical substance were (1) ability to penetrate the foci in which bacteria were active and to diffuse through devitalized tissue and blood clots without injury to living tissues, and (2) chemical and biologic compatibility with the sulfonamides and penicillin.

Although the two phases of this study were carried out jointly, as a matter of convenience they will be reported separately.

VEHICLES FOR THE TOPICAL APPLICATION OF ANTIMICROBIAL AGENTS

Carbowax Bases.—Previous experience with zinc peroxide in a water-soluble dressing with a carbowax base[35] suggested that this substance might prove a suitable vehicle for the effective local administration of the sulfonamides. The use of carbowaxes as carriers for zinc peroxide over a two-year period had confirmed their lack of toxicity and of irritating properties on repeated and prolonged applications to wounds.

The preparations tested for this purpose were carbowax 1540, carbowax 4000, and carbowax 6000,* and polyethylene glycol 300, and propylene glycol. Only a few studies were carried out with carbowax 6000. It has the consistency of marble, and even when mixed with propylene glycol and polyethylene glycol it had a tendency to cake on cooling. It is not yet available commercially.

Carbowax 1500, a polyethylene glycol of high molecular weight, has the consistency of petroleum jelly but is completely water-soluble. It is made by combining approximately equal parts of carbowax 1540 and polyethylene glycol 300. The resulting mixture spreads easily, furnishes a protective coating, can be adapted as a vehicle for a wide range of medicaments, and can be easily washed away with either warm or cold water without rubbing. Previous studies at the Mellon Institute[37] had indicated that this preparation is of very low toxicity and is no more allergenic when applied to the human skin than lanolin, petroleum jelly, glycerin, or any of the other agents commonly used as vehicles for drugs.

Carbowax 4000, a polyethylene glycol, is similar in consistency to hard paraffin but is completely water-soluble. Studies at the Mellon Institute had shown it to be nontoxic and nonallergenic.

Propylene glycol produces a very satisfactory base with carbowax 4000 and other carbowax mixtures. During World War II it became an accepted substitute for glycerine in many pharmaceutical preparations.

Carbowax 4000 base: Two bases were formulated. The first was made up of carbowax 1540, 40 to 50 parts, and polyethylene glycol 300, 60 to 50 parts. The variation in amounts depended on the season of the year.

This formula was found to have several drawbacks. In addition to the fact that the consistency of the mixture varies according to the season of the year, and that the proportions therefore had to be varied for each lot submitted by the manufacturer, there was a wide variation in the color and in the penicillin-inhibiting action of different batches of polyethylene glycol 300 and wide differences in the consistency and the inhibiting action of carbowax 1540.

The second formula, which consisted of carbowax 4000, 45 parts, and propylene glycol, 55 parts, was more satisfactory. The consistency of this formula varied insignificantly in different seasons of the year and the properties of the ingredients were found to be much more uniform. The carbowaxes are products of polymerization, and this process cannot be stopped at the same end point all the time. The end product, therefore, is always a mixture of carbowaxes of varying molecular weight but those in the higher range are more similar to each other in their physical state than are those in the lower ranges.

There were two minor drawbacks in this second formula. The first was that unless the mixture was stirred as it cooled, it tended to form a crust in the supercooled portions; this crusting did not occur if mixing were carried out properly. The second drawback was that in some patients, although there were no objective signs of irritation, the propylene glycol caused a transient burning or stinging sensation.

*The numbers refer to approximate molecular weights of the glycols.

A uniform method of preparation was used. A stock of carbowax 4000-propylene glycol base was made up, poured into jars, sterilized by heating at 140° C. dry heat for four hours, and was then stored at 5° C. When ointment was needed, the jars were placed in a water bath at 40° C. until the base had softened. The desired antibacterial agents were then added, with aseptic precautions, the ointment was stirred well, and the jars were again stored at 5° C. until they were used.

Sulfonamide Ointments.—When the solubility in carbowax of the various sulfonamides was tested, sulfanilamide, sulfathiazole, sulfaguanidine, sulfamethazine, and sulfamylon (marfanil) were found to be completely soluble in 5 to 25 per cent concentrations. Sulfapyridine was soluble up to only about 2 per cent. Sulfadiazine and sulfacetamide were insoluble in concentrations above 1 per cent. Dilution of the sulfonamide-carbowax solutions showed that the compounds remained in solution even if dilated up to 10 times with distilled water except for sulfathiazole, which was precipitated if it was diluted more than 7 times. The sulfathiazole-carbowax and sulfanilamide-carbowax solutions did not precipitate when the pH was lowered to between 3 and 4.

As the result of these factors, carbowax-sulfonamide ointments made it possible to apply greater concentrations of these drugs locally in soluble form, and, more important, permitted a more uniform distribution than is possible by the dusting technique.

These preparations were used clinically against susceptible organisms with satisfactory results as to prolongation of local action (Meleney). Sulfadiazine in concentrations of 3 per cent was combined with sulfathiazole when a combination of quick and slow action was desired. Sulfamylon was found to be least affected by sulfonamide-inhibitors, but all the drugs used in these carbowax preparations were inactivated by them in some degree.

Penicillin Ointments.—Penicillin, which is inactivated by propylene glycol, was found not to be inactivated when this glycol was combined with carbowax 4000. Why this preparation of carbowax exerts a protective action on penicillin is not yet understood, but batches of ointment containing 20 to 500 units of calcium penicillin per gram showed no loss of potency of the penicillin over a test period of 6 months when kept in the icebox at a temperature of 5° C., and some showed no loss of potency after twelve months. Except for one preparation, which showed some decrease in potency after one month, all other sodium penicillin preparations tested maintained their potency for four months or more when refrigerated at a 5° C. temperature. Since the activity of all preparations was found to fall off gradually after forty-eight hours at incubator temperature or after four days at room temperature, it is clearly important, when penicillin ointments are being used clinically, to keep them at icebox temperature and to change the dressings at least once daily.

Penicillin-carbowax preparations were sometimes applied directly to the wound and covered with fine meshed gauze or were applied as single- or double-layer impregnated gauze. Six of seven such dressings examined at

the end of twenty-four hours showed continued penicillin activity. Any possible loss of potency was compensated for by starting with high concentrations of penicillin (500 to 1000 units per gram of ointment).*

CRITERIA FOR IDEAL VEHICLES

Formulas with a carbowax base were found satisfactory for all practical purposes in a temperate climate but it was realized that they would not be satisfactory for very hot or very cold climates, since they do not remain soft and spreadable over a wide range of temperature. The individual constituents could be varied to a certain extent to meet climatic variations, but not to meet the full range. Further study is obviously indicated to determine modifications necessary to maintain the potency of the contained drug (particularly if the drug is penicillin) for a longer time at room or body temperature.

The Subcommittee on Infections and Burns of the National Research Council at a meeeting in 1943 set up the following criteria for an acceptable preparation containing antibacterial agents for local application: (1) It must be a single preparation; (2) it must be commercially available; (3) it must be packageable in the form of tubes and impregnated gauze; (4) it must be transportable in minimal bulk; (5) it must be quickly and easily applicable; (6) it must be sterilizable; (7) it must be physically stable, that is, extrudable from containers in temperatures down to −40° C., and must be resterilizable; (8) it must be chemically stable; (9) it must permit the incorporation and release of the sulfonamides, zinc oxide, penicillin, and other bacteriostatic agents; (10) it must not support bacterial growth; (11) it must be nontoxic, both locally and systemically; (12) it must permit drainage; (13) it must be nonescharotic; (14) it must be transparent to permit observation of the wound; (15) it must be nonadhesive; (16) it must be soothing; (17) its use must be compatible with the use of pressure dressings; (18) it must be readily removed by washing; and (19) finally, it must be approved by the Food and Drugs Administration.

The carbowax preparations studied met all these criteria except availability, nonadhesiveness, physical stability, and compatibility with pressure dressings. The two chief difficulties were the narrow temperature range, already commented on, and the adhesiveness of overlying dressings to wounds, caused by the ready solubility of the preparations in exudates, and their dilution by them, which tended to draw the drugs into the dressings. To make carbowax preparations fully effective it would be necessary to eliminate both these drawbacks.

Cellulose Carbowax Base.—The first real success in this study in broadening the temperature range of the carbowaxes came as a result of the discovery that propylene glycol could be gelled by methyl cellulose and certain other celluloses, gels of different consistencies being obtained by varying the amount and the viscosity type of the celluloses used. By this method a cellulose carbowax base was compounded which fully met the temperature requirements set by the Subcommittee on Infections and Burns of the National

*Later studies by Meleney showed that carbowax 4000-propylene glycol ointment is a satisfactory vehicle for the local application of p-chlorophenol, 9-aminoacridine hydrochloride, streptothricin, and streptomycin.

Research Council. This base, however, was not satisfactory because of its tendency to dissolve rapidly in the body fluids and to cause dressings to adhere to wounds.

The possibility of incorporating a grease in the mixture was then explored, but here a difficulty arose in meeting the requirement of sterilizability; carbowaxes were found not to form stable emulsions with greases. Eventually, however, this problem was also solved and the following ointment base was prepared:

Methocel 15 C.P.	2.5 per cent
Propylene glycol	
Carbowax 4000	22.5 per cent
Protopet (white petroleum jelly)	10.0 per cent
Vodol (lecithin)	0.2 per cent

This base seemed to come closest to what was desired for an all-purpose ointment. It had a uniform consistency over a wide range of temperature, from 0 to 55° C. and it could be sterilized by heating at 140° C. for four hours. It still, however, had certain shortcomings, the most important being some adherence to the wound if dressings were left intact for several days, probably as the result of an absorption of the water-soluble portions of the ointment. After this absorption had occurred, the methyl cellulose combined with the fibrinous exudate to make the overlying dressing stiff and somewhat adherent. Some patients complained, in addition, of an unpleasant burning sensation, though in no instance were there any objective signs of irritation. Further studies will be required to eliminate these difficulties.

After these studies had been made, some experience was reported by the National Formulary Committee in 1944 with a formula consisting of carbowax 1500, 55 parts, carbowax 4000, 20 parts, and propylene glycol, 25 parts. This base would seem to be a suitable vehicle for medicaments because: (1) It is nonirritating; (2) it is stable; (3) molds do not grow in it; (4) it is simple to prepare; (5) it can be removed by washing with water; (6) its pH value is approximately neutral; and (7) it has been shown by other workers not to react with the majority of drugs incorporated in it.

INVESTIGATION OF ANTIMICROBIAL AGENTS

Materials and Methods.—Attempts to find a chemical agent effective against gram-negative bacteria began with simple screening laboratory tests of a variety of agents obtained in the open market. The technique employed was as follows:

Five per cent human citrated blood was incorporated in 2 per cent beef infusion agar. Freshly prepared plates were flooded with a 1:100 dilution of an overnight beef infusion broth culture of the organisms to be tested.* Excess broth was drained by tilting the plates and was then removed with a pipette. After the surface had dried, 8 mm. holes were punched into the agar with a sterile cork borer and their edges were sealed with molten agar. Test substances were prepared in sterile distilled water or, when solubility in

*Stock cultures of *Pseudomonas aeruginosa*, *Proteus vulgaris*, and *Klebsiella pneumoniae*.

water was limited, in propylene glycol. Usually 0.2 c.c. of the test agent was placed in the cup.

Some plates were incubated immediately at 37° F. and were read after twenty-four hours. Other plates were placed in the icebox for six to twelve hours after being incubated at 37° F. for twenty-four hours. All tests were run in triplicate and the recorded results represent average readings.

It was arbitrarily determined that agents which produced a zone of inhibition against gram-negative bacteria around the agar cup with a radius of less than 5 mm. would be considered ineffective and would not be investigated further. The following compounds were eliminated by this criterion:

1. *Acids:* 2 per cent acetylsalicylic, 1 per cent ascorbic, 2 per cent para-aminobenzoic, 1 per cent parahydroxybenzoic, 1 per cent paranitrobenzoic, 1 per cent benzohydroxamic, 2 per cent alpha-hydroxyisobutyric, 2 per cent cinnamic, 4 per cent citric, 2 per cent lactic, 2 per cent phthalic, 1 per cent picramic, 1 per cent picrolonic, 0.7 per cent pyruvic, 1 per cent rosolic, 2 per cent sulfanilic, 1 per cent sulfosalicylic, 2 per cent terephthallic, 2 per cent thio-acetic, 1 per cent trichloracetic.

2. *Salts of acids:* 5 per cent sodium acetate, 0.1 per cent sodium azide, 1 per cent sodium benzoate, 8 per cent sodium benzyl monosuccinate, 1 per cent sodium cacodylate, 2.5 per cent sodium cinnamate, 5 per cent sodium citrate, 2 per cent potassium hydrophthalate, 5 per cent potassium iodate, 5 per cent sodium nitrate, 1 per cent sodium phthalate, 2 per cent sodium thioglycolate, 6 per cent sodium thiosulfate.

3. *Alcohols:* 70 per cent ethyl alcohol, absolute ethyl alcohol, 10 per cent mercaptoethanol, 5 per cent 2, 3-dimercaptopropanol "BAL."

4. *Amides:* 10 per cent acetamide, 10 per cent formamide, 2 per cent thio-acetamide, 2 per cent urea oxalate.

5. *Amines:* 0.5 per cent carboxymethoxylamine hemihydrochloride, 0.1 per cent benzalkonium chloride (Zephiran chloride), 0.1 per cent cetyl-pyridinium chloride (Ceepryn), 0.2 per cent dodecylamine ammonium lactate, 0.5 per cent hydroxylamine hydrochloride, 5 per cent methenamine, 0.1 per cent p-tert-octylphenoxyethoxyethyldimethylbenzylammonium chloride.

6. *Antibiotics:* 1 mg. per milligram gramicidin, 1 mg. per milligram tyrothricin, 250 units per milligram bacitracin, 500 units per milligram penicillin sodium.

7. *Bases, organic:* 1 per cent berberine, 1 per cent caffeine, 0.2 per cent 4:4′-diamidinodiphenoxypropane dihydrochloride (Propamidine), 8 per cent trimethyl-acethydrazid-ammonium chloride (Girard T).

8. *Dyes:* basic fuchsin, gentian violet, malachite green, methylene blue, (Nitroakridin), 0.1 per cent proflavine hydrochloride, sulfate, and monohydrochloride, 1 per cent phenylazo-alpha-a diaminopyridine monohydrochloride (Pyridium), toluidine blue.

9. *Heavy metal salts:* 2 per cent aluminum acetate, 1 per cent barium acetate, 1 per cent calcium lactate, 1 per cent copper sulfate, 5 per cent ferric chloride, 0.1 per cent mercury acetate, 1 per cent lead acetate, 5 per cent silver iodide.

10. *Detergents:* 0.1 per cent aerosol O.T., 0.1 per cent aerosol, 0.1 per cent tergitol-4, 0.1 per cent tergitol-8, 0.1 per cent catamine AO, 0.1 per cent triton 720, 0.1 per cent duponol IS.

11. *Oxidizing agents:* 0.1 per cent chloroazodin (Azochloramid), 1 per cent Dakin's solution, Ethiomine (addition salt of triethanolamine and hydriodic acid), Gram's iodine, 5 per cent Lugol's solution, Hyclorite (commercial Dakin's solution), 5 per cent potassium dichromate, 0.1 per cent potassium permanganate, 5 per cent potassium persulfate, 5 per cent tertiary butyl hypochlorite (in mineral oil), 20 per cent suspension zinc peroxide, medicinal.

12. *Organic mercurials:* 0.1 per cent 2-hydroxy-mercurifuran (Furmerane), 0.1 per cent ortho hydroxyphenylmercuric chloride (Mercresin), 0.1 per cent sodium dibrom-hydroxymercurifluorescein (Mercurochrome), 0.1 per cent sodium ethyl-mercurithiosalicylate (Merthiolate), 0.1 per cent 4-nitro-anhydro-5-hydroxymercury-o-cresol (Metaphen).

13. *Organic arsenicals:* 1 per cent tryparsamide.

14. *Sulfur compounds:* Alcohol sulfur, tergitol sulfur.

15. *Phenolic compounds:* Symmetrical p-chloro-dimethyl hydroxybenzene, p-tertiaryamyl hydroxybenzene (Amphyl), bismuth tribromphenate (Xeroform), chlorothymol, 0.05 per cent hexylresorcinol, phenyl semicarbamide, thiophenol, sodium chloro-2-phenylphenol (Dowicide C), sodium 2 chloro-4-phenylphenol (Dowicide D).

16. *Quinolines:* diodoquin, chiniofon.

17. *Sulfonamides:* 1 per cent sulfacetamide, 1 per cent sulfaguanidine, 1 per cent sulfamethazine, 1 per cent sulfanilamide, 1 per cent sulfapyridine, 2 per cent sodium irgamide, 2 per cent irgafen, 1 per cent silver sulfanilamide, 5 per cent Promin.

18. *Other compounds:* stilbestrol derivatives, synthetic vitamin K preparations, chlorophyll (Chloresium), barberry root extract.

Those agents which produced a zone of inhibition against gram-negative bacteria around the agar cup with a radius of 5 mm. or more were classified as possibly effective and were tested against numerous strains of organisms as well as for activity in the presence of pus and other body fluids. The following compounds fell into this category:

1. Quinolines: oxyquinoline benzoate, vioform.
2. Alcohol: 4 per cent benzyl alcohol.
3. Oxidizing agents: ethiomine, Lugol's solution.
4. Acridines: 9-aminoacridine hydrochloride.
5. Acids: 2 per cent acetic, 2 per cent para bromo-benzoic, 2 per cent alpha iodo-benzoic.
6. Phenolic compounds: 0.25 per cent *p*-chlorophenol.
7. Sulfonamides: sodium sulfadiazine, sodium sulfathiazole, sulfasuxidine.
8. Sulfamylon (marfanil, homosulfanilamide, mesudin).
9. Furans: 5-nitro-2-furaldehyde semicarbazone (Furacin).
10. Antibiotics: streptothricin, streptomycin.

In addition to the investigations outlined, certain possibly effective agents were evaluated for their effects on wound healing by Howes[14, 16] and some of the most promising were applied to infected wounds, to test their in vivo effects, by Meleney.

Quinolines.—Oxyquinoline benzoate and vioform were found to suppress the growth of gram-negative bacteria in concentrations ranging from 1:1,000 to 1:50,000 by the broth serial dilution test. Oxyquinoline benzoate is freely soluble in water but, like other soluble quinolines, it has the disadvantage of being unstable and extremely acid in solution. Vioform, on the other hand, is extremely insoluble, its solubility in water nearly paralleling the concentration required to effect the suppression of gram-negative bacteria in vitro in the absence of organic matter.

More important, the activity of the quinolines was found to be reduced nearly ten times in the presence of blood, pus, and body fluids. These compounds were toxic to cells on prolonged contact both in vivo and when tested by tissue culture techniques (Howes). The application of vioform in carbowax to open wounds was found to cause pain.

For these various reasons it was concluded in the final assessment that this group of compounds should be eliminated from further consideration in the search for an agent effective against gram-negative organisms.

Benzyl Alcohol.—Benzyl alcohol in 4 per cent concentration was found effective against gram-negative bacteria in excess of the 5 mm. radius zone, but there was considerable variation of susceptibility among the various strains of any single species. It was found to be toxic to tissues in culture and to be slightly inhibitory to epithelization in experimental wounds. For these reasons it was dismissed from further consideration.

Oxidizing Agents.—The iodine series of halogens was eliminated from further consideration as wound antiseptics, in spite of their inhibitory effect on gram-negative bacteria, for three reasons: (1) They coagulated proteins; (2) except in tissue-destructive concentrations their capacity for penetration into surrounding infected tissue was found to be minimal; (3) the strong reducing action of gram-negative bacterial pus rapidly neutralized them. Halogens are sometimes used in the therapy of infected wounds, but it is doubtful, in view of these disadvantages and limitations, that there is ever any justification for their use.

9-Aminoacridine Hydrochloride.—Tests of the bacteriostatic action of 9-aminoacridine hydrochloride against 168 strains of gram-negative organisms isolated from wound infections (Table I) showed that this compound ranks high in its capacity to suppress the growth of gram-negative bacteria in vitro. It was effective in vitro against all gram-negative organisms tested except *Bacillus pyocyaneus.* It proved slightly more bacteriostatic for aerobic gram-negative bacilli than proflavine. Proflavine solutions, however, are extremely acid and require neutralization with sodium bicarbonate before they can be applied to wounds. Moreover, proflavine is photolabile.

With the exception of *Pseudomonas aeruginosa,* for which concentrations of 1:1,000 were not always bactericidal, most species were found to be inhibited by 9-aminoacridine hydrochloride dilutions of 1:20,000. The bactericidal level for the *Escherichia coli* and Proteus strains tested was 1:10,000 concentration when the tubes were plated after twenty-four hours' incubation at 37° C. Differences between the concentration used for therapeutic application (1:1,000) and the effective bacteriostatic level were sufficiently great to allow for dilution in the wound. The addition of 20 per cent human plasma to the experimental setup made little difference in the amounts necessary for complete bacteriostasis.

Properties: In cup plate tests in blood and plain agar, 9-aminoacridine gave zones of inhibition greater in diameter than proflavine sulfate. It was readily soluble in water in 1:1,000 concentration, the pH of this concentration in distilled water being 6. It precipitated out in isotonic solutions of sodium chloride. Gauze sponges were not permanently stained by the 1:1,000 solution.

9-Aminoacridine proved compatible with both sodium penicillin and calcium penicillin in a concentration of 1:1,000 in distilled water or in carbowax 4000-propylene glycol ointment.

TABLE I. BACTERIOSTATIC ACTION OF 9-AMINOACRIDINE HYDROCHLORIDE AGAINST 168 STRAINS OF GRAM-NEGATIVE ORGANISMS*

		CONCENTRATIONS NECESSARY FOR COMPLETE BACTERIOSTASIS						
ORGANISMS	NUMBER OF STRAINS	MORE THAN 1:5000	1:5000	1:10,000	1:25,000	1:50,000	1:75,000	1:100,000
Esch. coli	55	0	0	5	32	15	2	1
Coli variants	12	0	0	4	4	0	3	2
A. aerogenes	8	0	1	5	2	0	0	0
P. vulgaris	37	0	0	12	11	9	3	2
Ps. aeruginosa	43	34	5	3	1	0	0	0
E. typhosa	2	0	0	0	0	1	1	0
K. pneumoniae	2	0	0	2	0	0	0	0
Achromobacter	6	0	0	2	1	3	0	0
Micrococci	3	0	0	2	0	1	0	0
Total	168	34	6	35	51	29	9	5

*The inoculum consisted of 0.05 c.c. of an overnight culture of the test strain in 5 c.c. of beef infusion broth at pH 7.2.

Clinical use: During World War II several British and Australian hospital units[24] found 9-aminocridine a potent antiseptic in the treatment of infected wounds and recommended its use with sulfathiazole in a proportion of 1:100 as a dusting powder. Other British workers,[25] however, demonstrated that acridines caused some tissue destruction.

For the purposes of this study 9-aminoacridine was prepared in an aqueous solution and in a carbowax base, in both the proportion being 0.1 per cent. In clinical testing it proved effective in eliminating *Escherichia coli* and Proteus from infected wounds but of only inconstant value in removing *Pseudomonas aeruginosa.* In spite of its apparently bacteriostatic properties in wound suppuration, the wounds in which it was used appeared sluggish and the rate of healing was retarded. For this reason further studies were not carried out, though this fact does not exclude the possibility that 9-aminoacridine may be

of occasional value in ridding granulating wounds of certain types of gram-negative bacteria.

Acids.—Three acids were found promising by the blood agar cup plate test, namely, acetic acid, para-bromobenzoic acid, and alpha-iodobenzoic acid. All three were of approximately the same order of effectiveness against gram-negative bacteria, but the latter two were eliminated from further consideration because they are hemolytic, expensive, and in the rare chemical class.

Acetic acid, which also is hemolytic, was introduced into clinical practice in 1916, when Taylor[39] showed that excellent clinical results followed its use in a dilute solution in wounds, and that it was usually effective in eliminating *Ps. aeruginosa*. The popularity of acetic acid in a 1 or 2 per cent solution has been sustained, though further investigation has revealed that it was somewhat less effective against *Ps. aeruginosa* than it had originally been believed to be. It is common knowledge that the activities of this organism may be suppressed and its pigmenting properties may be interrupted while the organisms themselves remain in the wound, and that a break in treatment may be followed by their vigorous regrowth. The explanation of the unevenness of results seems to be the in vitro demonstration that it takes at least 15 minutes for acetic acid to inhibit *Ps. aeruginosa* and that in wounds, unless puddling occurs or frequent changes of dressing are possible, it is difficult to achieve an adequate concentration for even this length of time.

It was found in this investigation that if acetic acid were buffered with sodium acetate to achieve a pH of about 4.0 (acetic acid 3 per cent, sodium acetate 4 per cent) results were better, and the combination acted more effectively over a longer period of time, than when the two agents were used separately. Shortly after this demonstration was made, it was learned that a commercial preparation of buffered acetic acid, sodium diacetate, was available, and a liberal supply was secured for testing purposes.

Sodium diacetate is a white powder, with the odor of vinegar, which is freely soluble in water and which is extremely stable if kept in vapor-proof containers. Industrial experience had showed it to be of great value in the prevention of mold- and rope-formation in bakery products, for which purpose it was reported greatly superior to vinegar, propionic acid, and other mold inhibitors previously used. Not the least of its advantages is its low price.

Clinically, sodium diacetate, when used in 5 per cent concentration in carbowax, proved highly effective against *Ps. aeruginosa* in wounds and in infections of the ear. It has the same capacity for separating and removing sloughs in third degree burns as pyruvic acid preparations have, and it costs about one-thirtieth as much. As the result of this study, therefore, sodium diacetate is recommended for the therapy of all conditions previously treated by unbuffered acetic acid.

Phenolic Compounds: p-Chlorophenol.—Of the halogenated phenols tested in vitro, *p*-chlorophenol seemed to give the greatest promise for clinical use. The work of Klarmann and his associates[18] on *p*-chlorophenol, *p*-bromophenol,

and *p*-iodophenol was repeated, but it was found that under the conditions of this experimental study, differences in bacteriostatic activity were too small to offset the increase in toxicity which accompanied the increase in the weight of the halogen atom. N-amyl-p-chlorophenol, 4-chloro-o-phenyl phenol and 0-(2,3 dichloropropyl) phenol were also studied but the margin between the concentration necessary for bacteriostasis and the maximum solubility of these compounds in water was found to be too small to make their use practical. All the attention was therefore focused on *p*-chlorophenol.

Properties: *p*-Chlorophenol was found to be readily soluble at room temperature in an isotonic solution of sodium chloride in a concentration of 1:200. It proved active in the presence of organic matter. When the agar cup plate method was used, it diffused into the seeded medium and caused zones of inhibition of growth. It is suitable only for local application. Its systemic toxicity, when it was injected subcutaneously into mice, was found to be 0.6 mg. per gram of body weight, which would make the minimum lethal dose for man in the concentration used for therapeutic application (0.25 per cent) 40 Gm. or 16 kg. of ointment. When *p*-chlorophenol was applied to experimentally produced wounds of the rabbit's ear in the concentration used clinically there was no appreciable inhibition of healing (Howes).

Tests of the bacteriostatic and bactericidal action of *p*-chlorophenol against 177 strains of gram-negative organisms isolated from wound infections (Table II) showed that the bactericidal level was very close to the bacteriostatic level. In no instance, when the tubes were plated after twenty-four hours' incubation at 37° C., were viable organisms found in the 1:1,000 dilution of *p*-chlorophenol in beef infusion broth.

p-Chlorophenol in a concentration of 0.25 per cent proved compatible with sodium or calcium penicillin in isotonic solutions of sodium chloride or in the carbowax 4000-propylene glycol base.

Clinical Use: Sinus tracts were irrigated with *p*-chlorophenol in 0.25 per cent concentration in isotonic sodium chloride solution. For local applica-

TABLE II. BACTERIOSTATIC ACTION OF P-CHLOROPHENOL AGAINST 177 STRAINS OF GRAM-NEGATIVE BACTERIA*

ORGANISM	NUMBER OF STRAINS	CONCENTRATION REQUIRED FOR COMPLETE BACTERIOSTASIS		
		1:1000	1:2000	1:3000-1:5000
Esch. coli	57	6	36	15
Coli intermediate	12	1	10	1
A. aerogenes	8	0	7	1
P. vulgaris	38	7	29	2
Ps. aeruginosa	44	5	23	16
Achromobacter	6	1	1	4
B. alkaligenes	3	0	0	3
S. alcalescens	2	0	1	1
E. typhosa	2	0	0	2
K. friedlanderi	2	0	0	2
Micrococci	3	0	0	3
Total	177	20	107	50

*The inoculum consisted of 0.05 c.c. of an overnight culture of the test strain in 5 c.c. of beef infusion broth at pH 7.2.

ation to wound surfaces the same concentration was used in carbowax 4000-propylene glycol ointment, applied directly or impregnated in fine mesh gauze (Meleney).

The use of *p*-chlorophenol in this manner in wounds infected with gram-negative organisms gave gratifying results. *P. vulgaris, Ps. aeruginosa, Esch. coli, E. typhosus,* and a gram-negative coccus were all promptly eliminated. In only two instances, both of chronic osteomyelitis, did the pyocyaneus bacillus fail to respond promptly to the local application of *p*-chlorophenol. The explanation in these cases was probably the physical configuration of the wounds, in both of which contact of the preparation with all infected surfaces was impossible. The compatibility of *p*-chlorophenol with penicillin made it a particularly valuable antibacterial agent in controlling penicillinase-producing gram-negative organisms in mixed infections in which penicillin-sensitive organisms were also present.[28]

In none of the cases in which *p*-chlorophenol was used in 0.25 per cent concentration was there any evidence of a local or general toxic reaction, though some patients complained of a slight burning sensation for a short time after the application was made.[28]

Sulfonamides.—Sulfadiazine and sulfathiazole in 1 per cent concentration were found almost equally effective against approximately one-third of the strains of gram-negative bacteria tested. Sulfaguanidine, sulfanilamide, sulfamethazine, and sulfacetimide were less constantly effective, and sulfasuxidine had only a slight inhibitory effect on all strains tested. The question naturally arises as to why the sulfa drugs should be so ineffective when they are applied to wounds topically and so effective in the inhibition of bacteria in the gastrointestinal tract. The work of Landy and his associates[20] throws some light on the matter. Their studies showed that gram-negative bacteria synthesize para-aminobenzoic acid in readily measurable amounts and that this acid is not retained in the cells but is excreted into the media. The quantity produced by bacteria varies among the strains of given species under apparently identical conditions, a fact which seems to explain why certain strains of gram-negative organisms are susceptible to the sulfa drugs and why others definitely are not. It seems extremely likely that the synthesis of para-aminobenzoic acid by these bacteria plays some part in the degree of their resistance to sulfonamides.

It was observed soon after their introduction that the sulfonamides are usually ineffective in the presence of abscesses and necrosis of tissue, the reasons postulated being the presence in products of tissue breakdown of large amounts of sulfonamide antagonists. The large amounts of these antagonists in such tissues, and the relatively small amounts in serum, for example, would explain the marked difference in therapeutic response between rapidly spreading infections and localized purulent foci, in which sulfonamide levels are generally too low to cope with the antagonists present in them.

Since concentrations of the drug equivalent to levels in the blood can be achieved by parenteral administration not only on wound surfaces, but also

in surrounding tissues, systemic administration seems more rational than local administration, both because the latter method is considerably less effective and because it may also give rise to frequent reactions from skin sensitization.

Carpenter,[4] Klein,[19] and Thatcher[40] reported that sulfadiazine and sulfathiazole show in vitro a cumulative antibacterial effect with penicillin, streptomycin, or both, and that patients treated with these combinations of drugs show no untoward effects. The clinical efficacy of combined sulfonamide and streptomycin therapy in acute brucellosis and of combined penicillin and sulfonamide therapy in many other infections is now well established. This special property of sulfadiazine has made it a valuable adjuvant to the antibiotics in the management of certain types of infection. Further studies of the combined effects of the sulfonamides and antibiotics are now in progress.

Sulfamylon.—Sulfamylon (marfanil, homosulfanilamide, mesudin) was recovered by the British from captured German units during the African Campaign (1942) of World War II under the name of marfanil. Marfanil[30] (sulfabenzamine hydrochloride) differs from sulfanilamide in that a methylene group has been inserted between the benzene ring and the 4-amino group. It is a white crystalline material freely soluble in water. Solutions are weakly acid (pH 5.0).

Because of the alteration in the benzene molecule, the antibacterial properties of sulfamylon are not inhibited by para-aminobenzoic acid and its mode of action therefore probably differs from that of the common sulfonamides. It was found to be effective in vitro against anaerobic organisms, in concentrations of 1:300 to 1:1,000, and also against aerobic staphylococci and streptococci. Its greatest effectiveness against gram-negative bacteria was on *Pr. vulgaris* and *Esch. coli*. *Ps. aeruginosa* was only inconstantly suppressed when concentrations of 1:500 were used. This agent therefore has much greater activity in vitro than the sulfonamides.

Tissue culture studies (Howes) showed sulfamylon to be relatively nontoxic. Applications to the conjunctiva of rabbits in concentrations up to 2 per cent were found to be nonirritating. Local applications to experimentally produced wounds in rabbits were well tolerated and caused no appreciable delay in wound healing. Sulfamylon did not seem to be inactivated by pus or by products of tissue degradation.

Applications to fresh wounds of 5 per cent sulfamylon in solution with streptomycin indicated that this mixture is a valuable aid to the usual surgical measures in the treatment of wounds (Howes).[14, 15]

Sulfamylon was found to be ineffective when given by mouth. Apparently it is deaminated and oxidized in the body and the resulting compound is devoid of antibacterial action.

Clinically 5 per cent sulfamylon in carbowax was found useful in the treatment of wound suppuration caused by polybacterial flora of predominantly gram-negative etiology (Meleney).

Nitrofurazone.—Nitrofurazone (furacin) is a substituted furan compound whose chemical formula is 5-nitro-2-furaldehyde semicarbazone. It is not

soluble in much less than 5,000 parts of water; its solubility in carbowax is in excess of 1 per cent. It was found to be effective in vitro against a variety of gram-negative and gram-positive bacteria, in concentrations of 1:20,000 to 1:75,000. It showed the least bacteriostatic activity against *Pseudomonas aeruginosa* and *Diplococcus pneumoniae*. It apparently had no hemolytic effect on red blood cells. In cup plate tests it diffused out into blood and plain agar and caused inhibition of growth when the plates were seeded with *Esch. coli* or Proteus organisms. The addition of 10 to 20 per cent human plasma to the beef infusion broth used for in vitro tests for bacteriostatic action did not appreciably alter the results.

When 5-nitro-2-furaldehyde was combined in 0.2 per cent concentration with calcium penicillin in amounts of 250 units per gram in carbowax-propylene glycol ointment, there was no appreciable loss of bacteriostatic activity by either agent over a two-month test period.

The report of the Council on Pharmacy and Chemistry of the American Medical Association[31] when nitrofurazone was accepted as a topical wound dressing for admission to New and Nonofficial Remedies in 1947 sums up the experience with the agent in this investigation:

> Nitrofurazone is useful for topical application in the prophylaxis and treatment of superficial mixed infections common to contaminated wounds, burns, ulceration and certain diseases of the skin. It may be useful as an adjunct to surgery in the preparation of areas for skin grafting and in the treatment of osteomyelitis. Daily application for periods of one month or longer may produce a local reaction in a small percentage of cases. Sensitivity or intolerance to its local use has been occasionally observed and may be cause for its discontinuance. Because of this, continuous applications for periods as long as five days may be capable of producing sensitization. Photosensitization from sunlight has not been encountered. Variant bacterial strains showing induced resistance to sulfathiazole, penicillin or streptomycin are as susceptible to nitrofurazone as their parent strains. Induced resistance to the aforementioned agents does not entail resistance to nitrofurazone.
>
> Systemic toxicity due to absorption of the compound is considered unlikely. Clinical studies indicate that the ingestion of 1 to 3 Gm. daily for long periods is fairly well tolerated by the majority of human subjects, but until more conclusive evidence of its mode of action and chemotherapeutic value becomes available its internal use cannot be recommended.
>
> Dosage.—Nitrofurazone is used topically in an ointment-like base containing a concentration of 1:500 (0.2 per cent). It is applied locally either directly or to dressings that cover the infected area. The base is water soluble but liquefies at body temperature and may thus require special coverings to maintain effective contact with certain areas to which it may be applied. Dressings may be reinforced with cellophane or similar material, and petrolatum gauze may be used for a barrier to limit the absorption into the dressing. On exposure to light, the bright yellow nitrofurazone turns dark brown. This is not associated with any ill effects and may be avoided by covering with light dressings.

Streptothricin.[42]—Tests of the bacteriostatic action of streptothricin hydrochloride against 110 strains of gram-negative organisms freshly isolated from wound infections (Table III) revealed a great variation in the suscepti-

bility of individual strains of the same species. Initial testing was carried out with a broth with a pH of 7.3. When broth with a pH of 7.8 to 8 was used, strains of *Esch. coli,* Proteus and *B. pyocyaneus* proved two and three times more sensitive to the bacteriostatic action of this agent. The addition of 10 per cent human plasma to the medium did not appreciably affect the action of streptothricin in vitro.

When streptothricin in the amount of 250 units per gram was combined with calcium penicillin in the amount of 250 to 500 units per gram in carbowax 4000-propylene glycol ointment, there was no loss of titer in either agent after four months' storage at 5° C.

TABLE III. BACTERIOSTATIC ACTION OF STREPTOTHRICIN HYDROCHLORIDE AGAINST 110 STRAINS OF GRAM-NEGATIVE BACTERIA*

ORGANISMS	NUMBER OF STRAINS	CONCENTRATION	COMPLETELY INHIBITED STRAINS 25 UNITS PER C.C.	50 UNITS PER C.C.	75 UNITS PER C.C.	100 UNITS PER C.C.	DRUG RESISTANT STRAINS
Esch. coli	35	11	10	8	2	2	2
Coli intermediates	8	4	2	1		1	
A. aerogenes	5	1	2	1		1	
P. vulgaris	23	1	1	5	4	7	5
Ps. aeruginosa	29	2	4	5	4	4	10
E. typhosa	1	1					
K. pneumoniae	1	1					
Achromobacter	5	4	1				
Micrococci	3	3					
Total	110	28	20	20	10	15	17

*The inoculum consisted of 0.05 c.c. of an overnight culture of the test strain in 5 c.c. of beef infusion broth containing 0.5 per cent sodium chloride with a pH of 7.3.

Clinical Use: It has been shown that doses of streptothricin necessary to protect animals against gram-negative and experimental infections, while successful in that objective, later were responsible for the death of a significant number of animals.* Since the toxic factor could not be separated from the antibiotic itself, streptothricin has been withdrawn from consideration for the systemic use of infections in man. It was applied locally in infected wounds, ulcers, and burns (Meleney), but this method of testing was also discontinued when streptomycin was discovered, streptomycin acting similarly to streptothricin but being much less toxic.

COMMENT

The search just outlined for agents effective against gram-negative bacteria was inspired chiefly by the effectiveness of the sulfonamides and of penicillin against gram-positive microorganisms. In an extensive survey of drugs and chemicals of different classes, considerable success was scored with sodium diacetate, *p*-chlorophenol, sulfamylon furacin, and streptothricin, and somewhat less success with oxyquinoline benzoate, 9-aminoacridine hydrochloride, and sulfadiazine and sulfathiazole.

The chemical and biologic dissimilarity of the compounds with which these successes were obtained is striking. Sodium diacetate presumably acts

*These studies were carried out in the laboratories of Merck & Co., Inc., Rahway, N. J.

by altering the substrate, that is, by lowering the pH to a degree which is incompatible with propagation of *Ps. aeruginosa*. *p*-Chlorophenol has a cytotoxic, and possibly a detergent, action; 9-aminoacridine and oxyquinoline are cytotoxic. The mode of action of sulfamylon remains to be elucidated. The sulfonamides act by interfering with certain metabolic functions of the bacterial cell. Streptothricin presumably also influences cell metabolism and reproductive capacity. Furacin is believed to act on some phase of cell metabolism, but the exact mechanism is not yet clearly understood.

The over-all screening tests in this study were made with the conventional antiseptic and chemotherapeutic agents, as well as with certain unusual agents, all selected more or less at random. They included acids, salts of acids, alcohols, amides, amines, antibiotics, organic bases, dyes, salts of heavy metals, anionic and cationic detergents, halogens and oxidizing agents, organic mercurials, organic arsenicals, sulfur compounds, insoluble quinolines, selected types of sulfonamides, and a variety of miscellaneous compounds. With none of the compounds tested was any significant agent discovered of potential clinical value in the therapy of gram-negative bacterial infections.

Sodium diacetate, which is buffered acetic acid, was found to be successful after topical application in ridding surface wounds of *Ps. aeruginosa* (pyocyaneus) infections. It also was found to have the capacity, which acids in general possess, of hastening the separation of sloughing tissue in third degree burns. It did not produce untoward systemic reactions and even after prolonged local use it did not significantly retard wound healing. Sodium diacetate has the additional advantage of being cheap.

p-Chlorophenol was found to be quasi-specific, that is, it proved about equally effective against gram-positive and gram-negative bacteria. It was also found to be fungistatic. Neither sodium diacetate nor *p*-chlorophenol has, to date, given any evidence of being allergenic nor of being particularly irritating to the skin surrounding open wounds in which it has been used.

Sulfamylon proved ineffective against clinical infections of *Ps. aeruginosa* origin but suppressed the growth of other gram-negative bacteria and of aerobic and anaerobic gram-positive bacteria. Howes[15] has reported its successful use in the prophylactic treatment of open wounds and reports have also been made of its value, both prophylactically and therapeutically, in ophthalmologic and otolaryngologic conditions. It is inactivated after oral administration and can be used only topically. At the present time sulfamylon is not commercially available.

Furacin, like sulfamylon, proved ineffective against *Ps. aeruginosa* infections but proved extremely successful bacteriostatically against other gram-negative bacteria and also against gram-positive organisms. Numerous reports attest its effectiveness as a topical wound antiseptic. It can be used only by topical application.

The sulfonamides remain as potential bacteriostatic agents against gram-negative bacteria. They have proved effective after oral administration and their capacity for diffusion into body exudates is high. Recent experiences

have shown important combined or cumulative action when the sulfonamides and streptomycin or the sulfonamides and penicillin have been used in combination.

The quinolines and 9-aminoacridine, while effective, proved too destructive to tissues to make them of practical clinical use except in selected cases.

Streptothricin, the only antibiotic available when this investigation was begun which showed promise against gram-negative bacteria, was eliminated from the investigation when other studies showed it to be toxic on both local and parenteral administration.

The topical application of antiseptics to wounds may be necessary under certain circumstances *because of the unlikelihood of achieving adequate concentrations by parenteral administration.* With these exceptions, the therapeutic emphasis for the present must remain on the systemic use of suitable agents. Topical application is undesirable for the following reasons:

1. The variety of bacteria likely to be responsible for infection, and
2. The variable effects of drugs upon infecting bacteria, there being no agent available to act as an umbrella for them all at once.
3. The variable absorbability of different drugs and their variable effects after dilution.
4. The poor penetrability of many drugs, as the result of their proteolytic action.
5. The toxicity of many drugs to tissue cells.
6. The inhibition of such agents as the sulfonamides by the products of tissue degeneration or proteolysis.
7. The possibility that bacteria trapped in sclerosed tissue may receive inadequate concentrations of the drug, so that drug-fastness will develop.
8. The opportunities for contamination (cross infection and reinfection) during dressings.
9. The pain and inconvenience of topical applications.
10. The time-consuming nature of this method.

Note.—This study of vehicles for the local administration of the sulfonamides and other bacteriostatic agents, together with a search for an effective agent against gram-negative bacteria, was undertaken in 1942, when the candidate was an assistant resident in surgery at the Columbia-Presbyterian Hospital Medical Center (1940 to 1943). It was continued from that time through 1944, supported in part by a grant from the Office of Scientific Research and Development, and in 1945, under the auspices of the U. S. Army. The report is divided into two phases, the Columbia University College of Physicians and Surgeons-Presbyterian Hospital phase, and the U. S. Army phase.

Dr. Frank L. Meleney, who was the Responsible Investigator when the investigation was carried on by a grant from the Office of Scientific Research and Development, gave valuable advice and criticisms. Dr. E. L. Howes and his staff collaborated in the tissue culture studies and the experiments in wound healing with the compounds believed to merit full study. Miss Balbina A. Johnson performed many of the in vitro broth serial dilution tests.

The sodium diacetate used in this study was supplied by the Niacet Chemicals Division, United States Vanadium Corporation, Niagara Falls, N. Y. The 9-aminoacridine hydrochloride used was supplied by Mallinckrodt Chemical Works, St. Louis, Mo. The *p*-chloro-

phenol was supplied by the Eastman Kodak Company, Rochester, N. Y. The sulfamylon was supplied by the Winthrop Chemical Co., Inc., New York, N. Y. The nitrofurazone was supplied by Eaton Laboratories, Inc., Norwich, N. Y. The streptothricin was supplied by Merck & Co., Inc., Rahway, N. J. The carbowax bases were supplied by the Carbide and Carbon Chemical Company, Inc., New York.

REFERENCES

1. Abraham, E. P., and Chain, S.: An Enzyme From Bacteria Able to Destroy Penicillin, Nature **146:** 837, 1940.
2. Albert, A.: Chemistry and Physics and Antiseptics in Relation to Mode of Action, Lancet **2:** 633, 1942.
3. Altemeier, W. A.: Bacteriology of War Wounds (Collective Review), Surg., Gynec. & Obst. (Internat. Abstr. Surg.) **75:** 518-533, 1942.
4. Carpenter, C. M., Bahn, J. M., Ackerman, H., and Stokinger, H. E.: Adaptability of Gonococcus to 4 Bacteriostatic Agents, Sodium Sulfathiazole, Rivanol Lactate, Promin, and Penicillin, Proc. Soc. Exper. Biol. & Med. **60:** 168-171, 1945.
5. Colebrook, L., and Kenny, M.: Treatment of Human Puerperal Infections and of Experimental Infections in Mice With Prontosil, Lancet **1:** 1279-1286, 1936.
6. Colebrook, L., and Kenny, M.: Treatment With Prontosil of Puerperal Infections Due to Hemolytic Streptococci, Lancet **2:** 1319-1322, 1936.
7. Colebrook, L., Buttle, G. A. H., and O'Meera, R. A. Q.: The Mode of Action of P-Aminobenzene Sulfonamide and Prontosil in Hemolytic Streptococcal Infections, Lancet **2:** 1323-1326, 1936.
8. Domagk, G.: Eine neue Klasse von Desinfections Mitteln, Deutsche med. Wchnschr. **61:** 829-832, 1935.
9. Dubos, R.: Antimicrobial Agents of Biologic Origin, J. A. M. A. **124:** 633-636, 1944.
10. Fleming, A.: On the Antibacterial Action of Cultures of a Penicillium, With Special Reference to Their Use in the Isolation of B. Influenzae, Brit. J. Exper. Path. **10:** 226-236, 1929.
11. Garrod, L. P.: Action of Antiseptics on Wounds, Lancet **1:** 798, 845, 1940.
12. Herrell, W. E.: Penicillin and Other Antibiotic Agents, Philadelphia, 1945, W. B. Saunders Company.
13. Howard, R. W.: Evaluation of Sulfonamide Ointment Bases, New England J. Med. **232:** 698-700, 1945.
14. Howes, E. L.: Prevention of Wound Infection by the Injection of Non-Toxic Antibacterial Substances, Ann. Surg. **124:** 268-276, 1946.
15. Howes, E. L.: Topical Use of Streptomycin in Wounds, Am. J. Med. **2:** 449-456, 1947.
16. Howes, E. L.: Rate and Nature of Epithelization in Wounds With Loss of Substance, Surg., Gynec. & Obst. **76:** 738-745, 1943.
17. Jenkins, H. P., and others: Further Studies on Preparation and Use of Sulfathiazole Ointment in Treatment of Burns, Surg., Gynec. & Obst. **80:** 85-96, 1945.
18. Klarmann, E., Shternov, V. A., and Gates, L. W.: Bactericidal and Fungicidal Action of Homologous Halogen Phenol Derivatives and Its "Quasi-Specific" Character; Derivatives of Orthochlorophenol, With Notes on Chlorine-Free Alkyl Phenol Derivatives, J. Lab. & Clin. Med. **19:** 835, 1934.
19. Klein, M., and Kimmelman, L. J.: The Correlation Between the Inhibition of Drug Resistance and Synergism in Streptomycin and Penicillin, J. Bact. **54:** 363-370, 1947.
20. Landy, M., Larkum, N. W., and Oswald, E. J.: Bacterial Synthesis of P-Aminobenzoic Acid, Proc. Soc. Exper. Biol. & Med. **52:** 338-341, 1943.
21. Lane, C. G., and Blank, I. H.: Vehicles in Topical Dermatologic Therapy, Arch. Dermat. & Syph. **54:** 497, 650, 1946.
22. Levaditi, C., and Vaisman, A.: Action curative et preventive du chlorohydrate de 4-sulfamido 2-4 dismino-azo benzene dans la streptococcie experimentale, Compt. rend. Acad. d. sc. **200:** 1694-1695, 1935.
23. McCulloch, E. C.: Disinfection and Sterilization, ed. 2, Philadelphia, 1945, Lea & Febiger.
24. McIntosh, J., Robinson, R. A. M., Selbie, F. R., Reidy, J. P., Blake, H. E., and Guttmann, L.: Sulphathiazole-Proflavine Powder in Wounds, Lancet **1:** 591-593, 1944.
25. McIntosh, J., Robinson, R. A. M., Selbie, F. R., Reidy, J. P., Blake, H. E., and Guttmann, L.: Acridine-Sulphonamide Compounds as Wound Antiseptics, Clinical Trials of Flavazole, With Clinical Reports, Lancet **2:** 97-99, 1945.
26. Meleney, F. L.: Study of Prevention of Infection in Contaminated Accidental Wounds, Compound Fractures and Burns, Ann. Surg. **118:** 171-186, 1943.
27. Meleney, F. L.: The Difficulty of Evaluating Drug Treatment in Surgical Infections, J. A. M. A. **124:** 1021-1026, 1944.

28. Meleney, F. L., Johnson, B. A., Pulaski, E. J., and Colonna, F.: Treatment of Mixed Infections With Penicillin, I. With Special Reference to Adjuvant Action of Parachlorophenol, J. A. M. A. **130**: 121-124, 1946.
29. Meleney, F. L.: Chemotherapy of Surgical Infections. In Treatise on Surgical Infections, New York, 1948, Oxford University Press.
30. Mitchell, G. A. G., Rees, W. S., and Robinson, C. N.: Marfanil and Marfanil Prontalbin, Lancet **1**: 627-629, 1944.
31. Nitrofurazone, Council on Pharmacy and Chemistry Report, J. A. M. A. **134**: 21, 1947.
32. Nitti, F., and Bovet, D.: Action du 4 sulfonamide 2-4 diamino benzol (prontosil) sur des infection streptococciques de la souria provoquees par des streptococques d'origine humaine, Compt. rend. Soc. de biol. **119**: 1277-1280, 1935.
33. Pulaski, E. J., Meleney, F. L., and Spaeth, W. L. C.: Bacterial Flora of Acute Traumatic Wounds, Surg., Gynec. & Obst. **72**: 982-988, 1941.
34. Pulaski, E. J.: Antisepsis and Disinfection in Surgery, Surg., Gynec. & Obst. (Internat. Abstr. Surg.) **84**: 107-121, 1947.
35. Reid, M. R., and Altemeier, W. A.: Peroxide Ointments, Ann. Surg. **118**: 741-750, 1943.
36. Selbie, F. R.: Microbial Resistance to Chemotherapeutic Drugs, Brit. M. Bull. **4**: 267-271, 1946.
37. Smyth, H. F., Carpenter, C. P., Shaffer, C. B., Seaton, J., and Fischer, L.: Some Pharmacological Properties of Polyethylene Glycols of High Molecular Weight (''Carbowax'' Compounds), J. Indust. Hyg. & Toxicol. **24**: 281-284, 1942.
38. Spink, W. W.: Sulfanilamide and Related Compounds in General Practice, Chicago, 1942, The Year Book Publishers, Inc.
39. Taylor, K.: Treatment of Bacillus Pyocyaneus Infection, J. A. M. A. **67**: 1598, 1916.
40. Thatcher, F. S., and MacLean, J. T.: Synergistic Action Between the Sulfonamides, Certain Dyes, and Streptomycin Against Gram-Negative Bacteria: Preliminary Report, J. Urol. **57**: 902-926, 1947.
41. Trent, J. C.: Historical Aspects of Aseptic Surgical Technic, S. Clin. North America **26**: 1035-1052, 1946.
42. Waksman, S. A., and Woodruff, H. B.: Streptothricin, A New Selective Bacteriostatic and Bactericidal Agent, Particularly Active Against Gram-Negative Bacteria, Proc. Soc. Exper. Biol. & Med. **49**: 207-210, 1942.

MASSIVE PENICILLIN THERAPY OF ABDOMINAL ACTINOMYCOSIS

GILMAN E. SANFORD, M.D., AND RICHARD O. BARNES, M.D., MEMPHIS, TENN.
(From the Surgical Service, Veterans Administration Medical Teaching Group, Kennedy Hospital)

ABDOMINAL actinomycosis has continued to present a challenge to the surgeon since the identification of the fungus sixty-one years ago. Although abdominal actinomycosis makes up only 18 to 22 per cent of the infections with actinomyces,[12, 23, 31] it is responsible for nearly 50 per cent of the fatalities from the disease.

Actinomycosis is an infection by a pathogenic species of actinomyces characterized by lesions composed of abundant granulation or connective tissue surrounding multiple areas of abscess formation.[14] Bacteriologic classification of the actinomyces has been difficult.[70] It has been complicated, from the medical viewpoint, by the presence of large numbers of nonpathogenic species. The most common pathogenic species have been classified by Keeney[37] as follows:

(1) *Actinomyces bovis (hominis,* Wolf-Israel, *israeli)*: Anaerobic or microaerophilic, gram positive, nonacid-fast
(2) *Nocardia asteroides*: Aerobic, acid-fast
(3) *Actinomyces madurae*

Actinomyces bovis is the most common cause of infection in man and also causes lumpy jaw in cattle. It has never been isolated from vegetation, but is commonly present in the mouth of man. *Nocardia asteroides* makes up approximately 10 per cent of the infections in man and is most common in pulmonary and brain lesions. *Actinomyces madurae* is the organism causing madura foot, and is not usually included in discussions of actinomycosis.

Actinomycosis is not a very rare disease. Cope reviewed 1,330 cases,[12] Sanford and Voelker 670,[38] and Kolouch and Peltier 1,236.[38] Several thousand articles have been published on the subject.[12] The number of reported cases is increasing each year, presumably because physicians are learning that all subacute and chronic abscesses should be examined for the presence of actinomyces. It is now realized that actinomycosis has a world-wide distribution[38] and that it is present with equal frequency in city and rural dwellers. Formerly it was thought, because of the ubiquitous presence of actinomyces on vegetation, that infection was incurred by chewing grass or straws, or from contact with cattle. It is now known that the organisms present on vegetation are harmless saprophytes,[12, 37] and there is no evidence to support contraction of the infection from cattle. There is abundant evidence, however, that pathogenic actinomyces make the human mouth their normal habitat.[55, 62] They have been isolated from pyorrhea pus, dental scum, salivary calculi, carious teeth, and tonsillar crypts.[76, 77] Thus, the modern concept is that actinomycotic infections are

Published with permission of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.
Received for publication, Aug. 10, 1948.

endogenous in origin.[43, 44, 62] There is no evidence to support the possibility of their transmission from man to man.[14]

There have been many diverse treatments for actinomycosis which have been well summarized and evaluated by Kolouch and Peltier.[38] Wagensteen[72] has re-emphasized the importance of surgery in the treatment of this disease, although the principles were first laid down by Waring in 1905.[38] Lyons[46] and others have emphasized the importance of adequate supportive therapy and frequent blood transfusions. But until the advent of modern chemo- and antibiotic therapy, the outlook for abdominal actinomycosis has been very poor. In 1929, Naeslund[55] reported 23 patients with abdominal actinomycosis, 22 of whom died within an average time of seven months after diagnosis. Kolouch and Peltier,[38] in their summary of the results of the treatment in 330 cases of abdominal actinomycosis, showed 30 per cent cured, 10 per cent improved, 54 per cent dead, and 6 per cent lost to follow-up. In this same study, treatment of 16 patients with sulfonamides showed 56 per cent cured, 18 per cent improved, 18 per cent dead, 4 per cent lost to follow-up. Their report included only 2 patients treated with penicillin, one of whom was improved and the other dead. We have found reports of 19 additional patients[8, 29, 31, 34, 47, 56] treated with penicillin, with 16 reported cured and three fatalities—a mortality of 15.8 per cent. There are numerous reports of cervicofacial actinomycosis successfully treated with penicillin,[16, 26, 28, 51, 73] and several reports of successful treatment of pulmonary actinomycosis.[35, 56, 59]

CASE REPORTS

CASE 1.—A 21-year-old white man was admitted to a hospital in March, 1946, with the history that on Feb. 1, 1946, he had an attack of severe peri-umbilical pain which later localized in the right lower quadrant. Roentgenograms were reported to show a large abdominal mass in the right lower quadrant which pushed the ascending colon upward and medially. An abscess was incised and drained in May, 1946, but its etiology not determined. The appendix had been removed during the patient's childhood and there was no evidence of tuberculosis or intestinal disease. He was discharged from the hospital with a draining sinus and his condition deteriorated progressively. He developed numerous abscesses with sinus formation in the right iliac and right lumbar regions. He was again hospitalized and numerous incisions and drainages were performed. In August, 1946, a diagnosis of abdominal actinomycosis was made. At this time, he received deep x-ray therapy, penicillin, sulfonamides, and repeated incision and drainage of abscesses. His condition continued to deteriorate and he was transferred to VAMTG Kennedy Hospital on Nov. 4, 1946.

Upon admission he appeared moribund. No further pertinent history was obtained except that he was discharged from the Navy in 1944 for rheumatic heart disease. Physical findings were: emaciation (weight 110 pounds, height 71 inches), pallor, weakness, dental caries, generalized edema most marked in dependant areas, moist râles in both lung bases posteriorly, enlarged heart, systolic and diastolic murmurs over mitral area, to-and-fro murmur over aortic area, blood pressure 134/58, palpable liver two fingers below costal margin, a sinus draining thick pus in middle of old right rectus scar, numerous draining sinuses over right iliac and right lumbar regions, an area of brawny induration 20 by 20 cm. over the right iliac region (Fig. 1), flexion contractures of both lower extremities, most marked on right (Fig. 2). Laboratory findings were: erythrocytes 2,000,000, hemoglobin 10.7 gm., leucocytes 4,550, serum protein 7 gm., albumin-globulin ratio 1.3. *Actinomyces israeli* was cultured from the drainage. The diagnoses of abdominal actinomycosis, mitral stenosis and insufficiency, aortic insufficiency, myocardial insufficiency, secondary anemia and cachexia were made.

The cardiac decomposition was treated with digitalis and mercurial diuretics. Vigorous supportive therapy was instituted consisting of high protein, high caloric, high vitamin diet with supplementary vitamins. The anemia was treated with numerous whole blood trans-

Fig. 1 (Case 1).—Right lumbar and iliac regions with multiple draining sinuses and areas of induration.

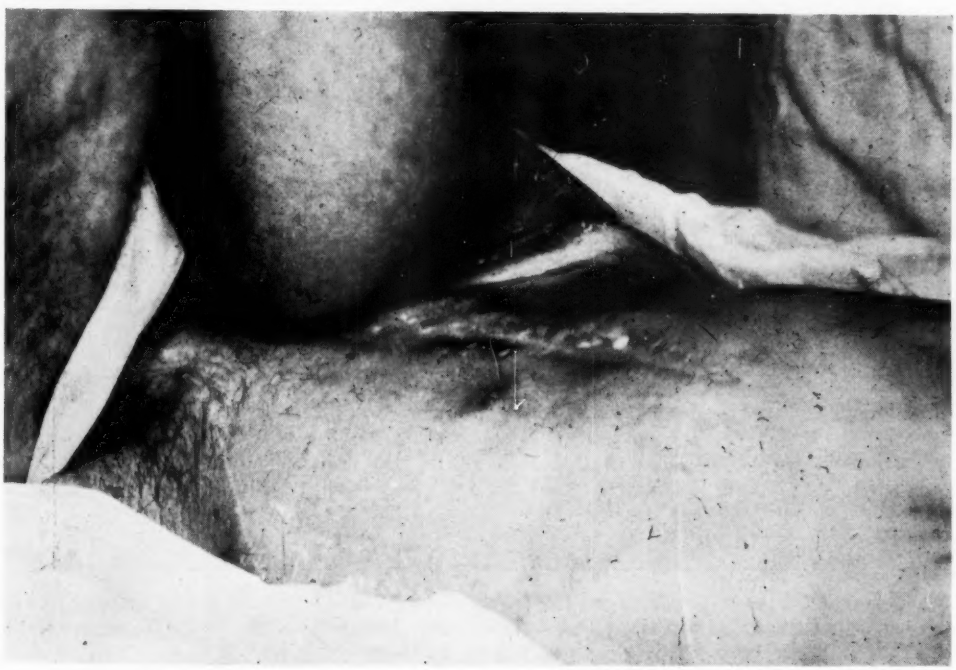


Fig. 2 (Case 1).—Patient supine with thighs extended as much as possible. Flexion contractures of both thighs most marked on the right. Draining sinus old right rectus scar.

fusions, 4,000 c.c. being administered in the first three weeks, and ferrous sulfate. The patient was placed on 100,000 units of penicillin intramuscularly every three hours and sulfadiazine 6 Gm. daily by mouth.

By Nov. 20, 1946, the patient's heart was compensated, but temperature ranged between 101° and 102° F. and he was still cachetic. On this date, the indurated area over the right iliac region was incised and a large abscess cavity containing thick, yellow pus was

Fig. 3.

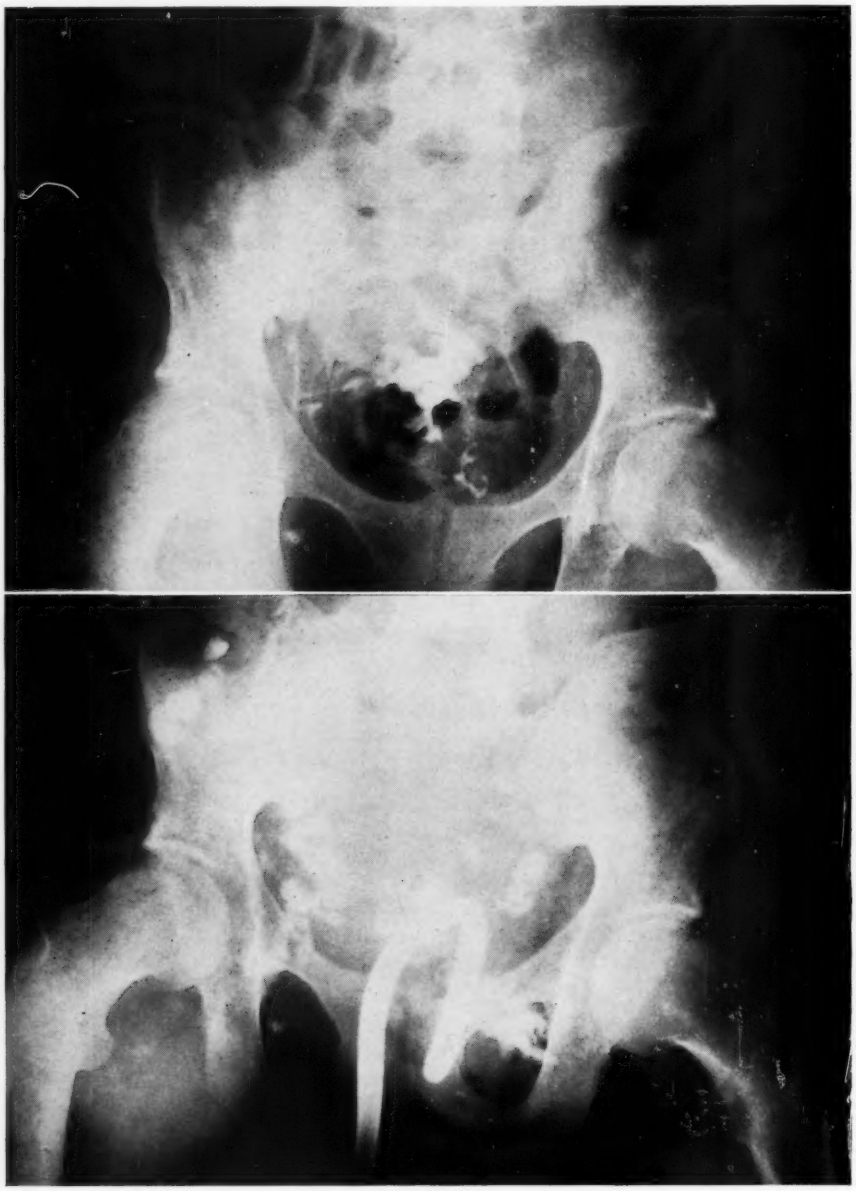


Fig. 4.

Fig. 3 (Case 1).—Diodrast injection of abdominal sinus May 5, 1947, showing connecting sinuses terminating at left ischial spine.

Fig. 4 (Case 1).—Diodrast injection of abdominal sinus May 26, 1947, showing extension of sinuses. Rectal tube is deflected by mass bulging into rectum.

drained. *Actinomyces israeli* was found on smear and culture of the pus. The patient slowly gained in strength and by December 15, the temperature remained normal except for an occasional rise relieved by incision and drainage of a newly formed abscess. *Actinomyces israeli* and *Staphylococcus aureus* were repeatedly cultured from the wounds. Attempts at determining the penicillin sensitivity of the actinomycoses were unsuccessful. Physical therapy was instituted for the contractures with improvement to the extent that the patient could be lifted to a wheel chair. In May, 1947, Diodrast injection of the sinus tracts showed multiple connecting sinuses extending from the region of the right iliac crest distally into a cavity along the right border of the sacrum which connected with a second cavity anterior to the hollow of the sacrum, and this cavity communicated with a third cavity at the left of the coccyx which terminated at the left ischial spine (Fig. 3). Injections done on May 26, 1947, showed an increase in diameter of the cavities and sinuses, and extension along the left border of the sacrum to the left ischium (Fig. 4). At this time, a mass became palpable by rectal examination. The patient failed to gain weight although every effort was made to

Fig. 5 (Case 1).—Diodrast injection of abdominal sinus July, 1947, showing further extension of sinuses and abscess formation in region of left ischium and neck of left femur.

improve his nutrition. In June, 1947, the patient began to complain of abdominal pain, vomited occasionally, and refused to move the left leg because of pain in the left hip. The anemia became more difficult to control and the pulse rate became increased. Diodrast injections on July 7, 1947, showed further extension of the cavity to the left ischial tuberosity and around the neck of the left femur (Fig. 5). Obviously the patient was losing ground. On July 14, 1947, an incision was made along the left border of the sacrum and coccyx unroofing a subcutaneous abscess in this region. The incision extended anteriorly just lateral to the anus and unroofed another abscess in the left ischiorectal space. The intervening involved tissue was removed. Another incision was made lateral to the left ischial tuberosity draining an abscess in this location which communicated with an abscess surrounding the neck of the left femur. The coccyx was then removed, establishing drainage for the pelvic abscess anterior to the sacrum. One of us (R.O.B.) suggested the trial of massive penicillin therapy since obviously all the infected tissue could not be removed in the presence of such extensive involvement. Up to this time (Nov. 4, 1946, to July 14, 1947), the patient had received 128,525,000 units of penicillin and 874 Gm. of sulfadiazine. During the next sixty-seven days (July 14 to September 19) he received 644,480,000 units of penicillin and 156 Gm.

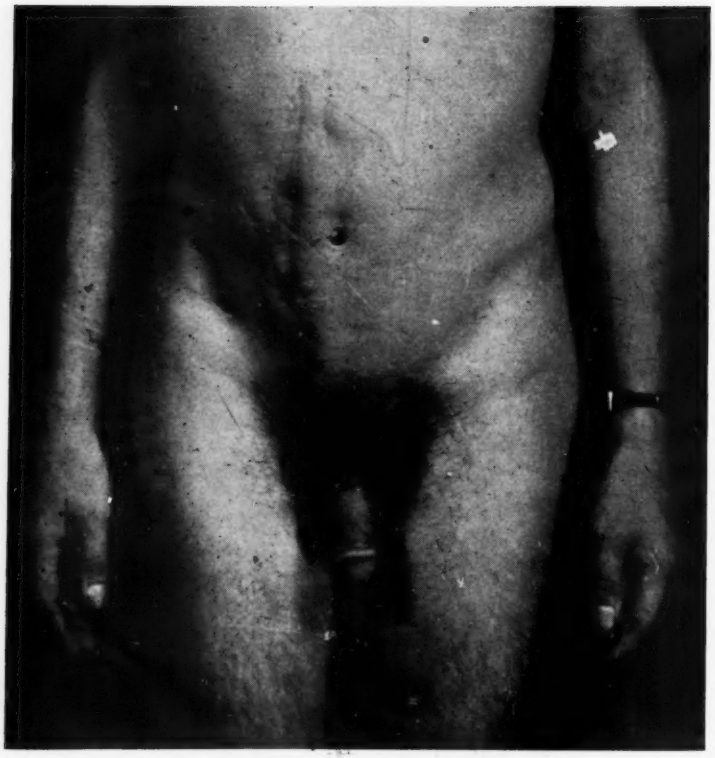


Fig. 6 (Case 1).—Photograph Oct. 13, 1947 (three months after institution of massive penicillin therapy). Abdominal sinus healed, nutrition excellent, and no contractures of the thighs.

Fig. 7 (Case 1).—Photograph Oct. 13, 1947. Scars of healed sinuses right iliac and lumbar regions.

of sulfadiazine. During the course of massive penicillin therapy, penicillin was administered as a continuous intravenous drip twenty-four hours a day, using 10,000,000 units per 1,000 c.c. of normal saline solution or 5 per cent glucose in distilled water. The wounds were irrigated daily with chlorophyll solution containing 1,000 units of penicillin per cubic centimeter, and sulfadiazine and supportive measures were continued. The response to this therapy was dramatic. There was little drainage from the wounds after the first twenty-four hours, and pain in the left hip, nausea, and vomiting disappeared. On the third postoperative day, the patient ate six eggs for breakfast and from that time on had an insatiable appetite. The continuous intravenous penicillin was continued for seven days with very little difficulty. During this time, the patient received between 30 and 40 million units daily. The blood penicillin level varied between 1 unit per cubic centimeter and 384 units per cubic centimeter. There was an occasional, mild phlebitis but by alternating arms, satisfactory veins were always available. The eighth day the penicillin dosage was reduced to one daily intravenous injection of 10,000,000 units in 1,000 c.c. normal saline solution by slow drip and 500,000 units intramuscularly every three hours. This dosage was continued until the twenty-fourth day, when the intramuscular injections were reduced to 200,000 units every three hours. On the thirty-fourth day, the daily intravenous injection was discontinued and the intramuscular injections were reduced to 100,000 units every three hours. This dosage was continued for four weeks. By September 15 (sixty-three days after initiation of massive penicillin therapy) the wounds were healed, there was no anemia, the patient had gained twenty-seven pounds, and he was walking normally with no evidence of contractures. He was discharged from the hospital on Oct. 13, 1947 (Figs. 6 and 7). This patient has been examined frequently, and ten months after discharge was well with no evidence of recurrence.

Comments.—Morton[54] has classified abdominal actinomycosis into three groups based upon physical signs:

1. Those resembling acute appendicitis, but with a residual abscess and/or fistula. The prognosis for this group is good.
2. Those characterized by a mass in the right lower quadrant with no obstruction. The mortality for this group is about 40 per cent.
3. Those with rapid extension in retroperitoneal cellular planes with psoas spasm, characterized by the flexed thigh. This group has been almost uniformly fatal, although Kolouch and Peltier[38] reported the cure of a case of this type by the combined use of penicillin, sulfonamides, adequate surgery, and supportive treatment.

Other isolated successful cases have appeared in the literature.[46, 49]

In accordance with Morton's classifications, Case 1 falls within Group 3 and a fatal outcome should have been expected. It is our belief that a fatality was prevented by the use of massive penicillin therapy.

Conflicting reports have been made of the sensitivity of actinomyces to penicillin. It apparently varies greatly with the strain encountered. Dobson and Cutting[16] found that a blood penicillin level of 0.5 to 1.5 units per cubic centimeter effectively inhibited actinomyces. But since a blood sulfa level of 10 mg. per cent also inhibited the organism, they concluded that sulfonamides were more practical therapeutic agents for the infection. Rosburg and Manlem[5] found two strains of actinomyces with the same penicillin sensitivity as the Oxford streptococcus. They found one strain four times more resistant, one strain eight times more resistant, and another sixteen times more resistant.

Abraham[2] found one strain with complete inhibition at a dilution of 1:1,000,000 with partial inhibition at a dilution of 1:2,000,000. Roberts[59] found one strain inhibited by 0.2 units of penicillin per cubic centimeter. Drake[17] studied seventeen strains and found one inhibited by 10 units of penicillin per cubic centimeter, three by 100 units per cubic centimeter, and twelve by 1000 units per cubic centimeter. Abraham and Miller[2] found inhibition at 0.1 units per cubic centimeter and no inhibition with sulfadiazine at 10 mg. per cent. Gottlieb[24] stated that concentrations much higher than 10 units per cubic centimeter must be tried before an organism is pronounced penicillin-resistant.

Factors other than resistance to penicillin are worthy of consideration since they must be considered in determining adequate penicillin dosages. It is felt by many that the growth of actinomyces is accelerated by the presence of secondary invaders.[14, 38, 54] Næslund[55] noticed a significant increased rate of spread of actinomycosis in the presence of bacteria causing an inflammatory reaction. Wagensteen[72] believed that concomitant invaders favor growth of the anaerobic actinomyces by reducing the oxygen potential. The theory of specific bacterial synergists has been advanced. Hassegawa[54] claimed to have demonstrated a definite symbiotic effect between actinomyces, *Staphylococcus aureus, Streptococcus viridans,* and *Spirochaeta dentium.*

Thus, in undertaking the treatment of actinomycosis, several factors must be considered. The anemia, cachexia, and malnutrition usually accompanying the disease must be combated by vigorous supportive therapy. Adequate surgery must be performed. In the past, these measures have not been adequate in treatment of abdominal actinomycosis. In addition to these measures, the proper use of chemo- and antibiotic therapy is, at present, the best available means of reducing mortality in this condition. Sulfonamides should be used in conjunction with penicillin for there is known sensitivity of some strains of actinomyces to sulfonamides, and these drugs often play an important part in combating secondary invaders. The determination of adequate penicillin dosages is complex. Sensitivity of different strains of actinomyces to penicillin varies. The sensitivity of the secondary invaders must also be considered. In addition, the pathologic process of the disease with its multiple abscesses surrounded by granulation tissue must be remembered. Gerber, Schwartzman, and Baher[21] have pointed out that it is necessary to obtain penicillin blood levels much higher than the inhibiting level in order to penetrate inflammatory foci.

Massive penicillin therapy has been most widely used in the treatment of bacterial endocarditis, although it has been used in the treatment of syphilis and other infections. Romansky[60, 61] mentioned one case of actinomycosis that responded to 40,000,000 units of penicillin daily. In most massive penicillin therapy, the penicillin has been administered by the continuous intravenous route. However, massive doses of penicillin have been given by continuous intramuscular injection and by intermittent intravenous or intramuscular injections.[58] The most troublesome feature of continuous intravenous administration has been the frequent occurrence of phlebitis. Phlebitis is thought, by some, to be due to impurities in penicillin preparations,[5] and it does seem less frequent with the newer preparations. There have been no toxic reactions reported and the incidence of allergic reactions does not seem to be any greater

with massive therapy than with standard dosages. The limit of human tolerance to penicillin has not been established. Lockwood[42] gave a child 100,000,000 units in twenty-four hours without reaction. Romansky[60] has given 40,000,000 units a day and stated that because of the lack of toxicity of penicillin there is no limit to the amount that may be given. Hunter,[32] Seaburg,[65] and Massey[48] have given 20 to 25 million units a day for as long as fourteen to sixteen days consecutively. Altemeier,[3, 4] Loewe,[42] and Bland and White[7] have given up to 10,000,000 units a day. Loewe[41] stated that the resistance of an organism is no deterrant to penicillin therapy since adequate levels can be maintained by massive dosages.

CASE 2.—A 28-year-old colored man was admitted to a hospital in March, 1946, complaining of right lower quadrant pain with nausea and vomiting, and an appendectomy was performed. The operative wound healed primarily and he was discharged in two weeks. In July, 1946, he was rehospitalized with a mass in the right upper and right lower quadrants of the abdomen, which he had first noticed a few weeks after the appendectomy. Incision and drainage were performed of both masses, which were apparently localized abscesses, and the patient was discharged with two draining sinuses. He was again hospitalized in November, 1946, because of persistently draining abdominal sinuses. At this time, he was given penicillin and the sinuses were irrigated with penicillin solution. Surgical excision of the sinus tracts was performed and the pathologic report was chronic inflammatory tissue. Drainage persisted from the site of the previous sinuses. On Jan. 22, 1947, the patient was transferred to VAMTG Kennedy Hospital.

Physical findings upon admission were: fair state of nutrition (weight 115 pounds, height 63 inches), temperature 100.6, pulse 95, blood pressure 130/85, a sinus draining yellow pus beneath the right costal margin anteriorly, a draining sinus in right flank just inferior to mid-portion of twelfth rib, a fluctuant mass in the right lumbar region at the level of the fourth lumbar vertebra. Laboratory studies showed 4,550,000 erythrocytes, 13.6 Gm. of hemoglobin, 10,600 leucocytes. Culture of drainage showed *Actinomyces israeli, Staphylococcus aureus*, and alpha streptococcus. Although frequent cultures were taken, actinomyces were not found again until July 21, 1947, when sulfur bodies were demonstrated, but staphylococci and streptococci were consistently present.

X-ray examinations revealed an elevated right diaphragm with slight pleural thickening over the right base and a normal gastrointestinal tract except for some distortion of the mucosal pattern and a tentlike outdrawing of the wall of the hepatic flexure of the colon (Fig. 8). X-ray studies after lipiodol injection of the sinus tracts showed the tracts leading to a large, grossly irregular cavity which appeared to be anterolateral to the liver (Fig. 9).

Initial treatment consisted of high caloric, high protein diet, supplemented by vitamins, penicillin in dosages of from 25,000 to 50,000 units intramuscularly every three hours, sulfadiazine 6 Gm. a day, incision and drainage of the abscess in the right lumbar region.

Drainage persisted from the sinuses, and the temperature rose daily to 101° F. After an initial weight gain, a slow weight loss began and anemia developed. On March 24, 1947, operation disclosed that all the sinus tracts converged under the eleventh rib and communicated with an abscess cavity in the right posterior subphrenic space. The subphrenic space was drained through the bed of the twelfth rib extraperitoneally. All sinus tracts were excised and as much of the involved tissue as possible was removed from the abscess wall. Pathologic examinations of the tissue showed it to be composed of vascular granulation tissue. Penicillin and supportive therapy were continued, and the anemia was treated by whole blood transfusions and ferrous sulfate by mouth. The abscess cavity was irrigated daily with chlorophyll solution containing 1000 units of penicillin per cubic centimeter. The patient became afebrile within one week and remained so for two weeks, when the temperature again became elevated and drainage from the abscess cavity became more profuse. On May 1, 1947, the drainage was revised and further débridement of the abscess cavity carried out. Again the patient's course seemed satisfactory. For six weeks he remained practically afebrile.

Then temperature elevations to 103° F. appeared and the patient began to lose weight. On July 21 the drainage was again revised and further débridement carried out. Tissue removed at this operation contained sulfur granules and *Actinomyces israeli* was readily cultured from it.

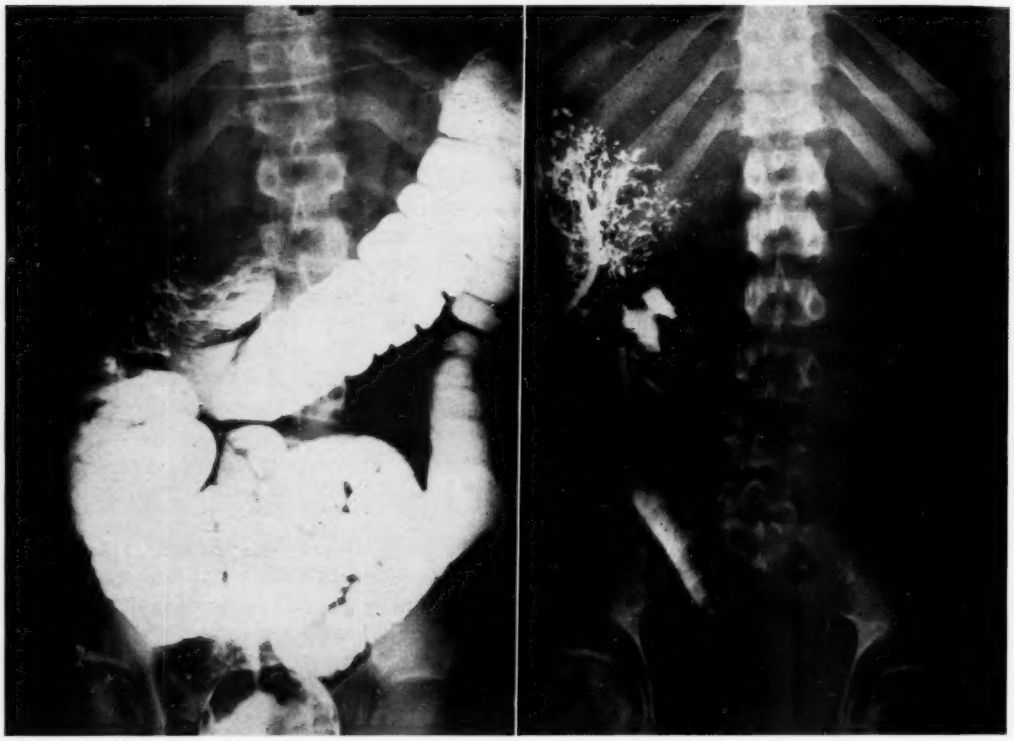


Fig. 8. Fig. 9.

Fig. 8 (Case 2).—Deformity of hepatic flexure of colon. Opacities above hepatic flexure are residual particles of lipiodol from previous injection of sinuses.

Fig. 9 (Case 2).—Lipiodol injection of sinus in right flank outlining subphrenic abscess.

The patient began to run a more septic course and lost weight more rapidly. By Aug. 2, 1947, weight was 109 pounds (admission weight 117 pounds). Up to this time (Jan. 22 to Aug. 2, 1947) the patient had received a total of 58,720,000 units of penicillin and approximately 1000 Gm. of sulfadiazine. It was decided to institute massive penicillin therapy and in the next forty-eight days he received 586,400,000 units of penicillin; 500,000 units of penicillin were given intramuscularly every three hours and 10,000,000 units in 1000 c.c. of normal saline solution were administered daily by slow intravenous drip. Sulfadiazine was continued in doses of 6 Gm. a day. The patient's temperature returned to normal by Aug. 8, 1947 (six days after institution of massive penicillin therapy), and remained normal thereafter. He began to gain weight. By September 11 (forty days after institution of massive penicillin therapy), the wound was completely healed. The intravenous penicillin was discontinued and the intramuscular doses reduced to 200,000 units every three hours. The patient was discharged on Sept. 19, 1947, with an erythrocyte count of 4,800,000, hemoglobin of 13.6 Gm., and weight of 129 pounds. For several months after discharge he was seen at monthly intervals, and there was no evidence of recurrence.

Comments.—Groves and Ochsner[23] reported two cases of subphrenic abscess due to actinomycosis, both of which terminated fatally. They were able to find only eight others in the literature, all of which were fatal. Shearburn[67]

reported one case with improvement after surgical drainage, but with recurrence after one year. Since that time, only one other case has appeared in the literature and it too terminated fatally.[50]

Although the two patients reported upon in this paper have been apparently cured in a comparatively short time after institution of massive penicillin therapy, it is too early to pass final judgment. Actinomycosis is noted for its tendency to recur. However, we believe that massive penicillin therapy played a major part in averting a fatal outcome in these two cases, and in bringing about an apparent cure within a remarkably short period of time.

SUMMARY

In the past, abdominal actinomycosis has been a highly fatal disease. Although it comprises only 18 to 22 per cent of human actinomycosis, it is responsible for nearly 50 per cent of the fatalities from the disease. However, with the advent of sulfonamides and penicillin and their use in conjunction with adequate surgery and supportive therapy, there has been some improvement in the prognosis of this disease.

A much greater improvement in the prognosis and considerable reduction in morbidity can be accomplished by the addition of massive penicillin therapy to the accepted methods of treatment of abdominal actinomycosis.

The course of events in two cases of severe abdominal actinomycosis indicates that infections of this type may not respond to penicillin therapy in rather large doses (800,000 units a day), sulfonamides, adequate surgery, and supportive therapy. These two patients received this therapy over prolonged periods (eight and nine months). There was improvement for a time and then progression of the disease. Their response to massive penicillin therapy was dramatic. One patient was apparently cured in sixty-three days after an illness of sixteen months. The other was apparently cured in forty-eight days after an illness of nine months. The only change in the treatment of these patients was the administration of massive doses of penicillin. Consequently, one may state with certainty that massive penicillin therapy has been responsible for the cures.

The apparent cure of an actinomycotic subphrenic abscess is noteworthy when the high mortality reported for these cases is considered. There have been eleven reported cases with only one patient alive after one year, and he had recurrence of the disease.

The method of administration and dosages for massive penicillin have been outlined in detail.

This report confirms the observations of others that massive doses of penicillin are not toxic even when given for relatively long periods.

Follow-up studies have shown cures of these two cases of one year's duration. The perfect health of the patients at this time leads us to regard these patients as permanently cured.

REFERENCES

1. Abraham, E. P., and others: Further Observations on Penicillin, Lancet **2**: 177, 1941.
2. Abraham, I., and Miller, J. K.: The In-vitro Action of Sulfonamides and Penicillin on Actinomyces, J. Bact. **51**: 145, 1945.
3. Altemeier, W. A.: Chemotherapy in Surgery, J. Missouri M. A. **44**: 803, 1947.
4. Altemeier, W. A., and Wadsworth, C. L.: Penicillin—Its Use in Surgery and Influence on Earlier Types of Chemotherapy, Surg., Gynec. & Obst. **84**: 54, 1947.

5. Barron, J. N., Mansfield, O. T., and others: An Investigation of the Therapeutic Properties of Penicillin, Brit. M. J. **1**: 513, 1944.
6. Bennett, J. G.: Actinomycosis With Lung and Liver Involvement, Brit. M. J. **1**: 121, 1944.
7. Bland, P. O., and White, P. D.: Bacterial Endocarditis; Experiences With Penicillin Therapy at the Massachusetts General Hospital, 1944-1946, New England J. Med. **237**: 349, 1947.
8. Bonney, G. L. W.: Actinomycosis of the Liver, Brit. J. Surg. **34**: 317, 1947.
9. Boston, R. L., and others: Persistence of Penicillin in the Cerebrospinal Fluid After Massive Intravenous Administration, Am. J. M. Sc. **214**: 50, 1947.
10. Chitty, H.: Recovery of Actinomycosis of the Liver, Brit. M. J. **1**: 115, 1944.
11. Conont, N. F., Martin, D. S., and others: National Research Council, Manual of Clinical Mycology, Philadelphia, 1945, W. B. Saunders Company.
12. Cope, Z.: Actinomycosis, New York, 1938, Oxford University Press.
13. Darling, G. C., and Eckoff, N. L.: Chemotherapy of Abdominal Actinomycosis, Lancet **2**: 707, 1946.
14. Davis, M. I. J.: Analysis of 46 Cases of Actinomycosis With Special Reference to its Etiology, Am. J. Surg. **52**: 447, 1941.
15. Dawson, M. H., and Hunter, T. H.: Treatment of Subacute Bacterial Endocarditis, Ann. Int. Med. **24**: 170, 1946.
16. Dobson, L., and Cutting, W. C.: Penicillin and Sulfonamides in Therapy of Actinomycosis, J. A. M. A. **128**: 56, 1945.
17. Drake, C. H.: The Action of Penicillin on Several Species of the Actinomycetales, J. Bact. **51**: 199, 1945.
18. Farris, E. M., and Douglas, R. V.: Abdominal Actinomycosis, Arch. Surg. **54**: 434, 1947.
19. Florey, H. W., and Florey, M. E.: General and Local Administration of Penicillin, Lancet **1**: 387, 1943.
20. Geiger, K. J.: Experiences in the Treatment of Subacute Bacterial Endocarditis, Am. Heart J. **33**: 736, 1947.
21. Gerber, I. E.: Schwartzman, G., and Baher, G.: Penetration of Penicillin Into Foci of Infection, J. A. M. A. **130**: 761, 1946.
22. Good, L. P.: Actinomycosis of the Abdomen, Arch. Surg. **22**: 307, 1931.
23. Groves, A. M., and Ochsner, A.: Actinomycosis of the Subphrenic Space, Am. J. Surg. **23**: 54, 1934.
24. Gottlieb, B., and others: H. Influenzae Meningitis in Infants Treated With Penicillin and Sulfonamides, Lancet **2**: 164, 1947.
25. Hall, W. E. B.: Sulfanilamide in Actinomycosis, J. A. M. A. **112**: 2190, 1939.
26. Hamilton, A. J. C., and Kirkpatrick, H. J. R.: Actinomycosis Successfully Treated With Penicillin, Brit. M. J. **2**: 728, 1945.
27. Hanes, F. M.: Actinomycosis, Internat. Clin. **1**: 206, 1942.
28. Hendrickson, G., and Lehman, E. P.: Cervico-facial Actinomycosis Successfully Treated by Penicillin Without Surgical Drainage, J. A. M. A. **128**: 438, 1945.
29. Herrell, W. E.: The Clinical Use of Penicillin, J. A. M. A. **124**: 622, 1944.
30. Hollenbeck, W. F., and Turnoff, D.: Actinomycosis Treated With Sulfadiazine, J. A. M. A. **123**: 1115, 1941.
31. Hollis, W. J., and Hargrove, M. D.: Actinomycosis, New Orleans M. & S. J. **99**: 499, 1947.
32. Hunter, T. H.: Treatment of Subacute Bacterial Endocarditis With Antibiotics, Am. J. Med. **1**: 83, 1946.
33. Jones, S. H., and Tichy, F.: Bacterial Endocarditis Treated With Penicillin, New England J. Med. **236**: 730, 1947.
34. Jones, T. E., and Brownell, T. S.: Treatment of Actinomycosis With Penicillin, Cleveland Clin. Quart. **12**: 32, 1945.
35. Kay, E. B.: Actinomycosis, Its Treatment by Pulmonary Resection in Conjunction With Chemotherapy, Ann. Surg. **124**: 535, 1946.
36. Keefer, C., Blake, F. G., and others: Penicillin in the Treatment of Infection, J. A. M. A. **122**: 1217, 1943.
37. Keeney, E. L.: Medical Mycology, M. Clin. North America **29**: 323, 1945.
38. Kolouch, F., and Peltier, L. F.: Actinomycosis, SURGERY **20**: 401, 1946.
39. Kolmer, J. A.: Penicillin Therapy Including Tyrothricin and Other Antibiotic Therapy, New York, N. Y., 1945, D. Appleton-Century Company, Inc.
40. Lockwood, J. S., White, W. L., and Murphy, F. D.: The Use of Penicillin in Surgical Infections, Ann. Surg. **120**: 311, 1944.
41. Loewe, L., and Eiber, H. B.: Subacute Bacterial Endocarditis of Undetermined Etiology, Am. Heart J. **34**: 349, 1947.
42. Loewe, L., Rosenblatt, P., Russell, M., and Alture-Werber, E.: The Superiority of the Continuous Intravenous Drip for the Maintenance of Effectual Serum Levels of Penicillin, J. Lab. & Clin. Med. **30**: 730, 1945.

43. Lord, F. T.: A Contribution to the Etiology of Actinomycosis, J. A. M. A. **57**: 9, 1911.
44. Lord, F. T.: A Contribution to the Etiology of Actinomycosis: The Experimental Production of Actinomycosis in Guinea Pigs, Boston M. & S. J. **163**: 82, 1910.
45. Lord, F. T., and Trevett, L. A.: The Pathogenesis of Actinomycosis, J. Infect. Dis. **58**: 115, 1936.
46. Lyons, C., Owen, C. R., and Ayers, W. B.: Sulfonamide Therapy in Actinomycotic Infection, SURGERY **14**: 99, 1943.
47. Lyons, C.: Penicillin Therapy of Surgical Infection in the U. S. Army, J. A. M. A. **123**: 1007, 1943.
48. Massey, F. C.: Massive Doses of Penicillin in the Treatment of Subacute Bacterial Endocarditis, Hahneman. Monthly **82**: 289, 1947.
49. Masson, D. M.: Abdominal Actinomycosis: Report of Two Cases With Clinical Cure, Proc. Staff Meet., Mayo Clin. **11**: 833, 1936.
50. Mallory, T. B., and others: Case Records of the Massachusetts General Hospital, Case Number 32262, New England J. Med. **234**: 870, 1946.
51. Meleney, F. L.: Recent Experiences With Penicillin in the Treatment of Surgical Infection, Bull. New York Acad. Med. **20**: 517, 1944.
52. Meleney, F. L.: The Difficulty of Evaluating Drug Treatment in Surgical Infection, J. A. M. A. **124**: 1021, 1944.
53. Miller, E., and Fell, E. H.: Sulfanilamide Therapy in Actinomycosis, J. A. M. A. **112**: 731, 1939.
54. Morton, H. S.: Actinomycosis, Canad. M. A. J. **42**: 231, 1940.
55. Næslund, C.: Experimentelle Studien über die Aetiologie und Pathogenese der Aktinomykose, Acta path. et microbiol. Scandinav., Supp. 6, p. 1, 1931.
56. Nichols, D. R., and Herrell, W. E.: Penicillin in the Treatment of Actinomycosis, Proc. Central Soc. Clin. Research, J. Lab. & Clin. Med. **32**: 1405, 1947.
57. Ogilvie, W. H.: Abdominal Actinomycosis Treated With Sulfapyridine, Brit. M. J. **2**: 254, 1940.
58. Peters, E. E., and Boston, R. L.: The Massive Intravenous Penicillin Therapy of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**: 522, 1947.
59. Roberts, J. E. H., and Tubbs, O. S.: Pleural and Pulmonary Suppuration Treated With Penicillin, Lancet **1**: 39, 1945.
60. Romansky, M. J.: The Current Status of Calcium Penicillin in Beeswax and Peanut Oil, Am. J. Med. **1**: 395, 1946.
61. Romansky, M. J.: The Current Status of Penicillin Therapy, V. A. Tech. Bull. TB 10-25, March 28, 1947.
62. Rosebury, T., Epps, L. J., and Clark, A. R.: Study of Isolation, Cultivation, and Pathogenicity of Actinomyces Israeli Recovered From Human Mouths and From Actinomycosis in Man, J. Infect. Dis. **74**: 131, 1944.
63. Scudder, S. T., and Deputy, R.: Acute Bacterial Endocarditis Due to Penicillin Resistant Streptococcus Hemolyticus, Northwest Med. **46**: 529, 1947.
64. Scull, C. B., and Caldwell, J. R.: Rheumatic Carditis With Congestive Failure: Presentation of a Case, Delaware State M. J. **19**: 115, 1947.
65. Seaburg, J. J.: Subacute Bacterial Endocarditis, Arch. Int. Med. **79**: 1, 1947.
66. Selbie, F. R., Simon, R. D., and McIntosh, J.: Bacteriological Aspects of Penicillin Therapy, J. Path. & Bact. **57**: 47, 1945.
67. Shearburn, E.: Actinomycosis of Stomach and Duodenum, SURGERY **14**: 38, 1943.
68. Smith, F. L.: Postoperative Treatment of Abdominal Actinomycosis, S. Clin. North America **10**: 171, 1930.
69. Tumulty, P. A., and Harvey, A. McG.: Experiences in Management of Subacute Bacterial Endocarditis Treated With Penicillin, Am. J. Med. **4**: 37, 1948.
70. Wakeman, S. A., and Henrici, A. T.: The Nomenclature and Classification of the Actinomycetes, J. Bact. **46**: 337, 1943.
71. Wakeman, S. A., and Woodruff, H. B.: Selective Antibiotic Action of Various Substances of Microbiological Origin, J. Bact. **44**: 373, 1942.
72. Wagensteen, O. H.: The Role of Surgery in the Treatment of Actinomycosis, Ann. Surg. **104**: 752, 1936.
73. Walker, J. M., and Hamilton, J. W.: The Treatment of Actinomycosis With Penicillin, Ann. Surg. **121**: 373, 1945.
74. Walker, O.: Sulfanilamide in the Treatment of Actinomycosis, Lancet **1**: 1219, 1938.
75. Weeks, K. D., and McClelland, W. S.: Hemorrhagic Smallpox—Report of Case With Recovery, Treated With Massive Doses of Penicillin, U. S. Nav. M. Bull. **47**: 707, 1947.
76. Weller, C. V.: Incidence and Pathogenesis of Tonsillar Concretions, Ann. Otol. Rhinol. & Laryngol. **33**: 79, 1924.
77. Wilkinson, H. F.: Pathologic Changes in Tonsils, Arch. Otolaryng. **10**: 127, 1929.
78. Zeller, W. W., and others: The Treatment of Bacterial Endocarditis With Penicillin and Streptomycin, M. Ann. District of Columbia **17**: 21, 1948.

THE EFFECT OF TEMPORARY RENAL VASCULAR OCCLUSION ON KIDNEY FUNCTION

J. R. Scheibe, M.D., E. Giraldi, M.D., and C. W. Vermeulen, M.D.
Chicago, Ill.

(From the Department of Surgery, University of Illinois College of Medicine)

IN SOME operations for the production of portacaval shunts, the venous return from the kidney has been temporarily occluded to facilitate the operative procedure. This temporary renal venous occlusion has been used to explain uremia following the operation, and occlusions lasting longer than ten minutes have been thought to incur serious renal damage.[1, 2]

We were unable to find any experimental observations upon the effect of temporary venous occlusion with the exception of some observations by Stoll and Carlson. They studied the period of anuria subsequent to occlusion of the renal vein of the dog for a period of fifteen minutes. No difference was found between venous or arterial occlusions of this duration. On the other hand, abundant evidence is available on the tolerance of the kidney to temporary occlusion of the entire renal pedicle or the artery alone. With this type of occlusion the rat kidney has been found to tolerate interruption of the blood flow for sixty minutes.[3, 4] Rabbits, dogs, and cats will withstand renal pedicle or arterial occlusion for 90 to 120 minutes, although in some instances fatal uremia occurs after temporary occlusion of such duration. [5-13]

PROCEDURE

Adult rats and dogs were used in this experiment. Preliminary unilateral nephrectomy was done on all animals. After complete recovery the animals were divided into groups and temporary occlusion of either the whole pedicle or the vein alone was carried out for varying periods of time. Temporary occlusion of the whole pedicle in the rat was done for periods of 30, 60, 90, 120, and 150 minutes. The vein alone was occluded for 30, 60, and 90 minutes. In the dog the whole kidney pedicle was occluded for 150 minutes while the renal vein was temporarily occluded for periods of 15, 60, 90, 105, and 150 minutes. The operative procedure for vascular occlusion was done through a small flank incision under nembutal anesthesia. The kidney was delivered, and the pedicle isolated and occluded with a small clamp. In the cases where the vein was to be occluded it was carefully isolated from the rest of the pedicle and the clamp applied to the vein alone.

The effect of these occlusions was determined in the rat by estimation of the blood urea nitrogen after an interval of forty-eight hours following the occlusion. In those cases where the dog was used, daily blood urea nitrogen determinations were made. In some animals blood urea clearances were determined at intervals following the operation. Routine urinalysis was done on all animals. All animals were autopsied following either death by uremia or

Received for publication, Nov. 13, 1948.

sacrifice. Histologic sections of the kidney were made in all cases. In a few instances thrombosis of the temporarily occluded vessel was found to have occurred, as evidenced by marked necrosis within the kidney and demonstration of occlusion of the vessel on autopsy.

RESULTS

The mean forty-eight hour blood urea nitrogen levels for each group of rats are shown in Fig. 1 and Table I. When the renal vein had been occluded for 30, 60, or 90 minutes, the mean forty-eight hour blood urea nitrogen levels were 27, 125, and 210 mg. per 100 c.c., respectively. Temporary occlusion of the whole renal pedicle for 30, 60, or 90 minutes gave mean forty-eight hour blood urea nitrogen values of 20, 27, and 49 mg. per 100 c.c., respectively. If,

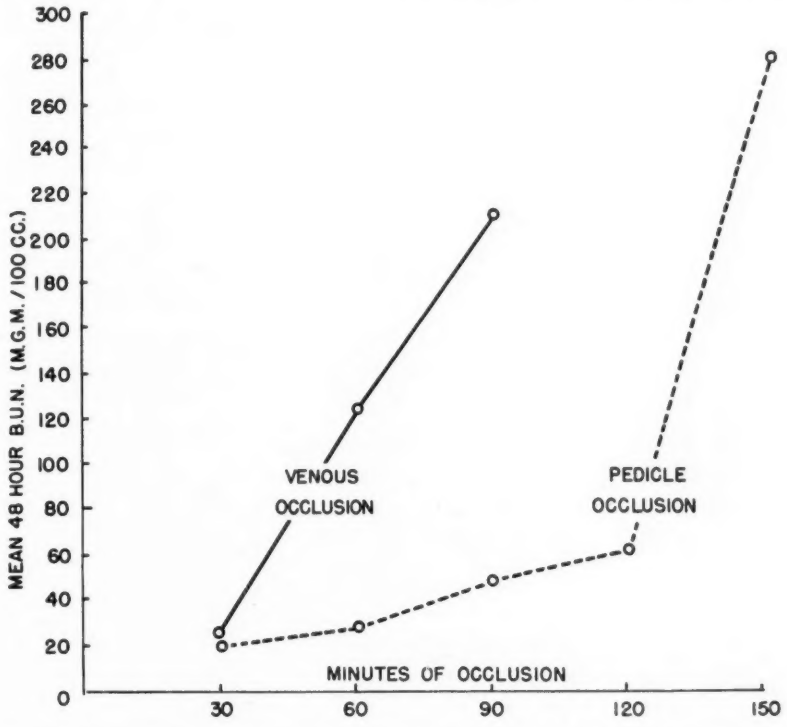


Fig. 1.—Graph comparing the mean urea nitrogen forty-eight hours after temporary renal venous occlusion and temporary renal pedicle occlusion in the rat.

however, the renal pedicle had been occluded for 120 or 150 minutes the respective mean blood urea nitrogen levels of 62 and 281 mg. per 100 c.c. were found. It is evident then that in the rat, occlusion of the entire renal pedicle for a period of 90 minutes can be well tolerated since the blood urea nitrogen following such occlusion is only approximately 50 mg. per cent. On the other hand, when the vein alone is occluded for a similar period of time the animal is extremely uremic within forty-eight hours and most of such animals die from uremia.

Urine examination in all groups of rats revealed relatively few findings. There were moderate numbers of red blood cells, a few white blood cells, some epithelial cells, and occasional granular or cellular casts.

TABLE I. MEAN FORTY-EIGHT HOUR BLOOD UREA NITROGEN LEVELS*

MINUTES OF VASCULAR OCCLUSION	NUMBER OF ANIMALS	MEAN 48 HR. B.U.N. (MGM/100 C.C.)
	Whole Renal Pedicle	
150	5	281.2 ± 44.8
120	9	62.9 ± 44.4
90	7	49.1 ± 21.9
60	10	27.7 ± 17.2
30	7	20.0 ± 6.8
	Renal Vein	
150	0	—
120	0	—
90	10	210.8 ± 41.2
60	12	125.3 ± 37.8
30	10	27.0 ± 9.0

*Experimental data comparing the mean blood urea nitrogen 48 hours after temporary renal pedicle occlusion and temporary renal venous occlusion in the rat.

The renal vein was temporarily occluded on five dogs for 150 minutes (see Table II). The mean highest blood urea nitrogen level was 136.2 mg. per 100 c.c. The urea clearance on one of these dogs twenty-four hours after occlusion was 12 per cent of the preocclusion urea clearance. As the animal recovered from azotemia the urea clearance gradually returned to normal in six days. With vein occlusion for two and one-half hours, two of the five animals died of uremia.

TABLE II. TEMPORARY RENAL VENOUS OCCLUSION*

MINUTES OF VASCULAR OCCLUSION	NUMBER OF ANIMALS	MEAN HIGHEST B.U.N. (MGM/100 C.C.)
	Whole Renal Pedicle	
150	4	73.4
	Renal Vein	
150	5	136.2
105	1	100.0
90	1	92.0
60	4	55.3
15	1	23.0

*Experimental data showing the relation of the mean highest blood urea nitrogen in temporary renal venous occlusion and temporary renal pedicle occlusion in the dog.

The renal vein was temporarily occluded on four dogs for sixty minutes. The average highest blood urea nitrogen in this group was 55.3 mg. per 100 c.c. with no mortality. The average urea clearance was 36 per cent of the preocclusion urea clearance with gradual return to normal in two to six days. Three additional dogs were used for temporary renal venous occlusion, one at each period of 15, 90, and 105 minutes. The resulting highest blood urea nitrogens were 23, 92, and 100 mg. per 100 c.c., respectively, with no mortality. The whole pedicle of the kidney on four dogs was occluded for 150 minutes and the average highest blood urea nitrogen was 73.4 mg. per 100 c.c. followed by recovery in every instance. The average urea clearance on these dogs was 35 per cent of the preocclusion urea clearance with gradual return to normal in two to three weeks.

Fig. 2.

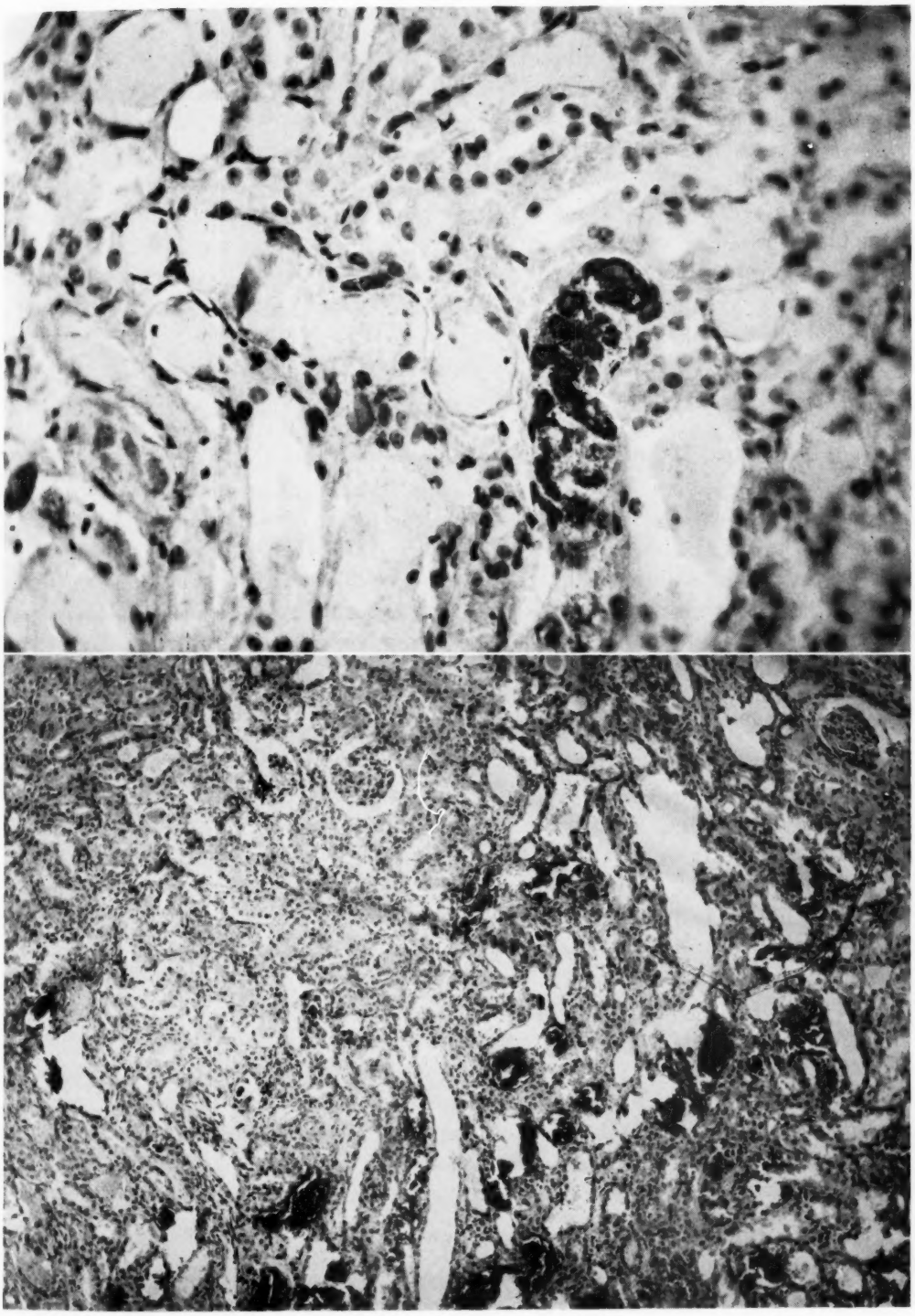


Fig. 3.

Fig. 2.—Photomicrograph of a rat's kidney forty-eight hours following a renal venous occlusion for 90 minutes. Tubular necrcsis with calcification is seen in the central portion of the picture. The forty-eight-hour blood urea nitrogen on this animal was 281 mg. per 100 c.c. (×400.)

Fig. 3.—Photomicrograph of a rat's kidney ninty-six hours following venuos occlusion for 60 minutes. The early appearance of calcium in the juxta medullary region is marked. (×100.)

The results in the dog, therefore, parallel the findings in the rat and show greater tolerance to whole renal pedicle occlusion than to isolated renal vein occlusion. The urinary findings on these sixteen dogs were exactly similar to those seen in the rat.

The pathologic findings, both gross and microscopic, were essentially the same for the dog and the rat. During venous occlusion the kidney became blue-black in color, very tense, and covered with a serous exudate. Upon removal of the clamp the tension rapidly disappeared. In contrast, when the renal pedicle had been occluded the kidney became pale, slightly softer than normal, and no serous exudate appeared.

With both venous and whole pedicle occlusion the microscopic changes are greatest in the proximal convoluted tubules. Depending upon the length of the temporary occlusion these changes progress to severe necrosis with calcification (see Figs. 2 and 3). Calcification occurs initially in the tubular epithelium of the proximal convoluted tubules and many "microcalculi" are seen in the distal tubules. The glomeruli and the distal convoluted tubules remain relatively unaffected except in that group of rats where the pedicle had been occluded for 150 minutes. In this group extensive necrosis of all elements of the kidney occurred. Where tubular changes occur, hyaline casts are common. Moderate round-cell infiltration is seen throughout the sections with a greater focal accumulation in the cortex.

DISCUSSION

The evidence would indicate that the renal vein may be occluded for 30 minutes in the rat, or 60 minutes in the dog without appreciable pathologic or functional change, whereas the whole kidney pedicle can be occluded for more than twice these periods of time without serious renal damage. The more rapid appearance of kidney damage where the renal vein has been occluded, as compared to whole pedicle occlusion, is striking and perhaps may be explained by the presence of greater capillary pressure associated with venous obstruction.[14]

The characteristic lesion produced by temporary occlusion of the renal vein or the renal artery is degeneration of the epithelium of the proximal convoluted tubule. The distal convoluted tubule and the glomeruli remain relatively unaffected except in more prolonged occlusion. This finding of greatest sensitivity to anoxia of the proximal convoluted tubule does not seem to be in agreement with Truetta's renal shunt theory of the etiology of "lower nephron nephrosis," where the distal convoluted tubule is considered to be affected selectively by cortical ischemia.

SUMMARY

1. The renal vein can be occluded for 30 minutes and the renal pedicle for 90 minutes in the rat, or twice these periods of time in the dog without significant renal damage.

2. Occlusion of the whole pedicle is less damaging to the kidney in rats and dogs than occlusion of the vein alone.

3. An incomplete occlusion of the entire pedicle causes more renal parenchymal damage than complete occlusion because there results a complete venous occlusion with incomplete arterial occlusion.

4. The suggestion that venous occlusion of the kidney for 10 minutes may result in fatal uremia is probably an overstatement.

REFERENCES

1. Welch, C. S.: A Technique for Portacaval Anastomosis (Eck Fistula), Surg., Gynec. & Obst. **85**: 492, 1947.
2. Prather, G. C.: Method of Hemostasis During Nephrostomy, J. Urol. **32**: 578, 1934.
3. Koletsky, S., and Gustafson, G. E.: The Effects of Temporary Cessation of Renal Blood Flow in Rats, J. Clin. Investigation **26**: 1072, 1947.
4. Emmel, V. M.: Mitochondral and pH Changes in the Rat's Kidney Following Interruption and Restoration of the Renal Circulation, Anat. Rec. **28**: 361, 1940.
5. Litten, M.: Untersuchungen über den haemorrhagischen Infarct und über die Einwirkung Arterieller anaemie auf das lebende Gewebe, Ztschr. f. klin. Med. **1**: 131, 1880.
6. Eisendrath, E., and Straus, D. C.: The Effect on the Kidney of Temporary Compression of Its Vessels, J. A. M. A. **55**: 2286, 1910.
7. Marshall, E., and Crane, M.: The Influence of Temporary Closure of the Renal Artery on the Amount and Composition of the Urine, Am. J. Physiol. **64**: 387, 1928.
8. Selkurt, E. E.: The Changes in Renal Clearance Following Complete Ischemia of the Kidney, Am. J. Physiol. **144**: 395, 1945.
9. Hübner, A.: Die temporare Abklemmung des Nierenstiels, Arch. f. klin. Chir. **132**: 665, 1924.
10. Scarff, R. W., and Keele, C. A.: The Effects of Temporary Occlusion of the Renal Circulation in the Rabbit, Brit. J. Exper. Path. **24**: 1947, 1943.
11. Van Slyke, D.: Effects of Shock on the Kidney, Tr. A. Am. Physicians **58**: 119, 1944.
12. Stoll, J. E., and Carlson, A. J.: The Anuria Following Temporary Anemia of the Kidneys, Am. J. Physiol. **67**: 153, 1923.
13. Mc Enery, E. T., Meyer, J., and Ivy, A. C.: Studies on Nephritis, J. Lab. & Clin. Med. **12**: 349, 1927.
14. Hinman, F., Jr.: The Rational Use of Tourniquets, Surg., Gynec. & Obst. **81**: 357, 1945.

DISLOCATIONS AND FRACTURE-DISLOCATIONS OF THE FOOT: TRANSFIXION WITH KIRSCHNER WIRES

EDWIN O. GECKELER, M.D., PHILADELPHIA, PA.

(From the Orthopedic Department, Hahnemann Medical College and Hospital)

DISLOCATIONS of the foot, either with or without fractures, are difficult to treat; unless reduced early and completely these injuries cause permanent pain and disability. As it is impossible to reduce most dislocations and fracture-dislocations of the tarsal and metatarsal bones by manipulation, operative treatment is usually necessary; however, even after the displaced bones have been exposed and the interposed ligaments have been retracted, it is difficult to keep them reduced. Tight casts should be avoided on account of the danger of circulatory disturbance, and if the plaster is molded in attempting to maintain reduction severe sloughing may occur from local pressure. Sutures of any kind are unsatisfactory for internal fixation, and in most instances nails and screws are too short; if nails or screws are used, a subsequent operation usually is necessary for their removal.

No references can be found in the literature which describe the use of Kirschner wires for internal fixation after reduction of dislocations and fracture-dislocations of the tarsal bones, although Gordon Murray has recently described the insertion of a Kirschner wire for fractures of the great toe. I have had complete success in treating these injuries by using Kirschner wires for fixation. This method is simple and effective.

TECHNIQUE

After exposing the bones the interposed ligaments first are retracted, and then the dislocation can be reduced easily by traction and gentle leverage. Next, while reduction is maintained and the wound still is open, one or more Kirschner wires are drilled through the skin at some distance from the wound, passing through adjacent bones for transfixion. It is important to hold the foot in the normal position while the bones are being transfixed; that is, without inversion or eversion. The wire should be drilled only as far as necessary for a firm hold, as it will not hold securely after it has been revolved excessively or if it has been inserted too far and then retracted. If the Kirschner wire does not maintain reduction completely and firmly, it should be withdrawn and reinserted before the wound over the displaced bones is sutured. The reduction and security of fixation can be checked by manipulation and direct visualization, as the incision is not closed until after the wires have been inserted. In cutting off the excessive length of a wire, the jaws of the cutters should be pressed close against the skin, and thus by picking up the skin the end of the wire will be covered.

When it is found necessary to produce ankylosis because of extensive fracture-dislocation, the articular cartilage should be removed before the wires are introduced. These wires do not interfere with arthrodesis; on the contrary, they hasten union of the opposing joint surfaces.

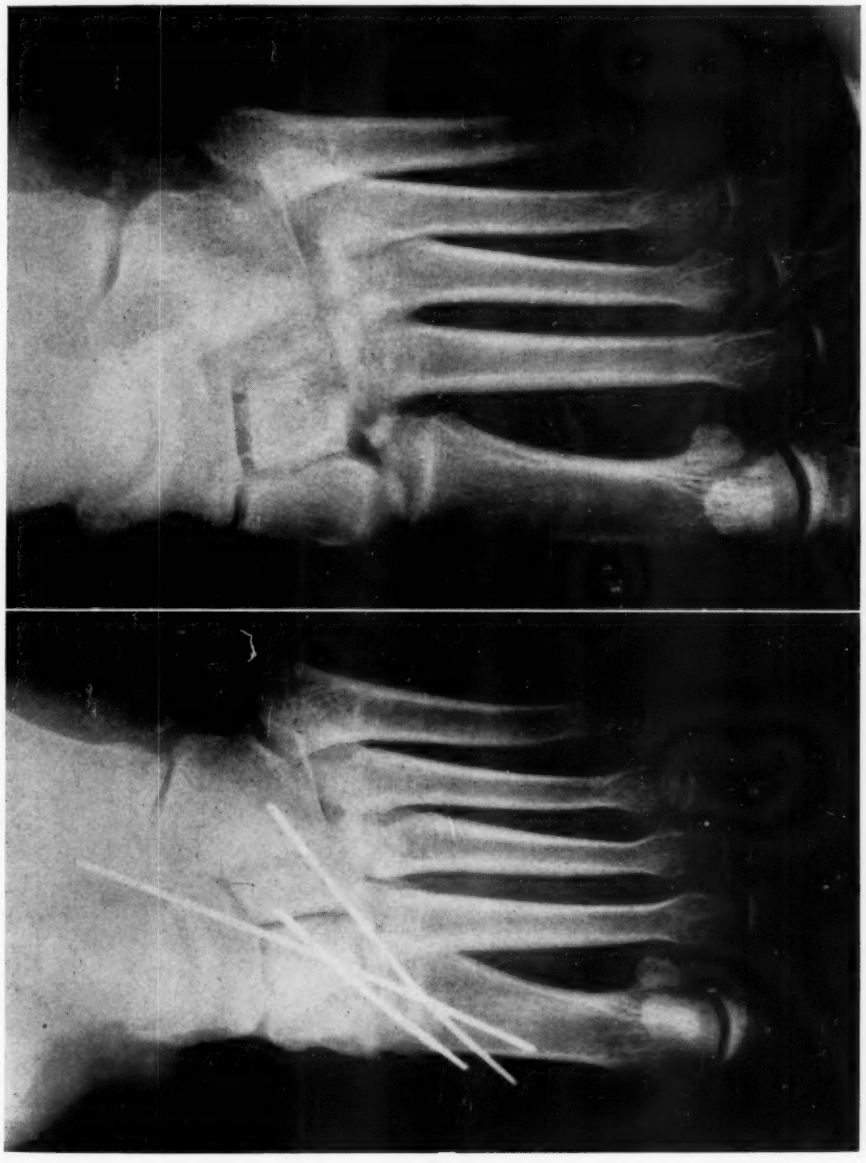
Received for publication, July 30, 1948.

After the wound has been closed a padded cast is applied, the plaster extending from the tips of the toes to below the knee, holding the foot in the neutral position.

FOLLOW-UP CARE

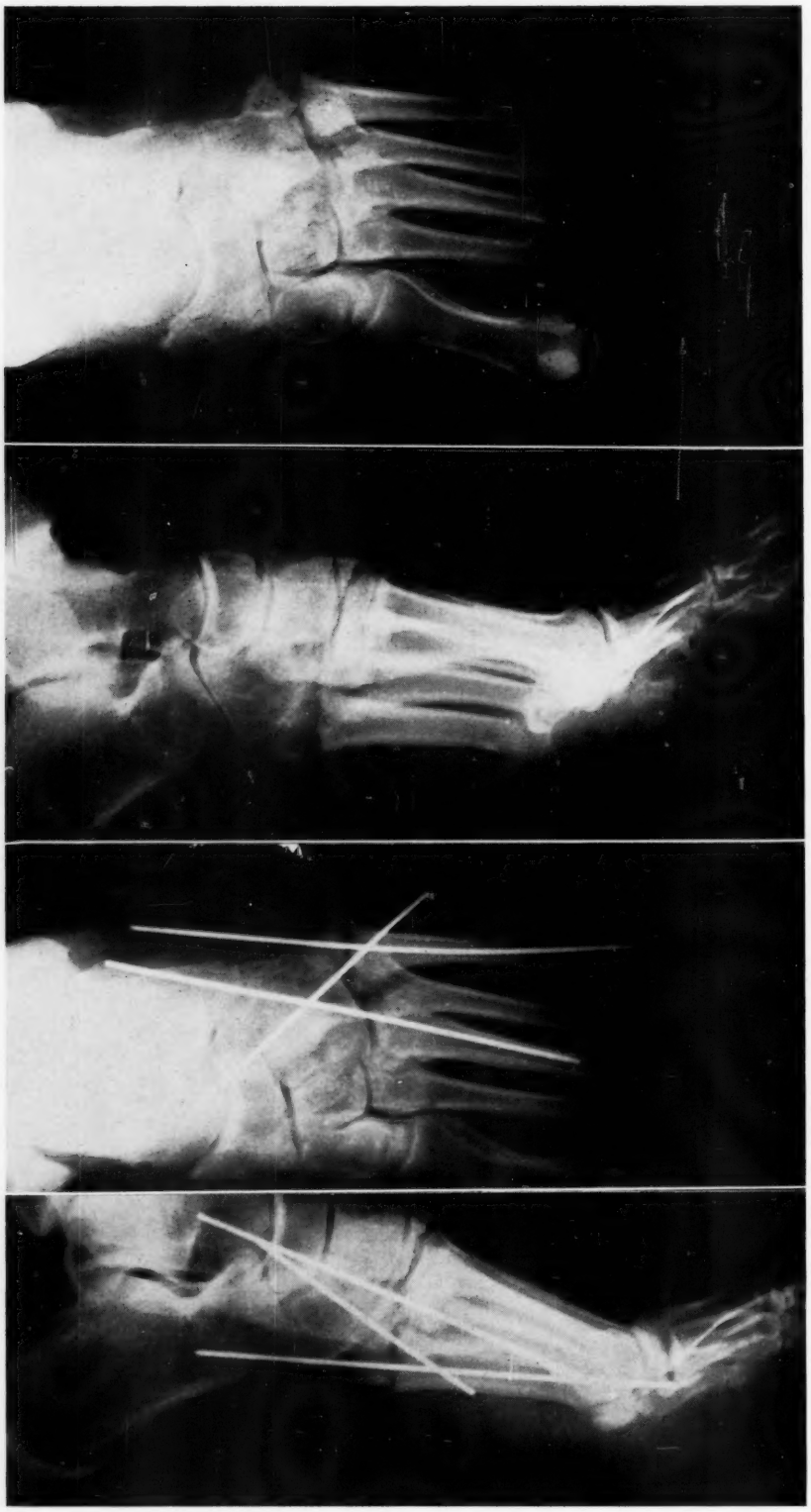
Kirschner wires placed in the foot will not migrate if they have been inserted securely. After several weeks the wires are exposed by nicking the skin, and are extracted with a pair of sterilized pliers. Minor cases do not need further immobilization after this time, but fracture-dislocations treated by arthrodesis must be held in plaster for several weeks after removal of the internal fixation. After the final cast has been removed an elastoplast or ACE

A.



B.

Fig. 1.—*A*, Tarsometatarsal dislocation. *B*, Dislocation reduced openly and fixed with Kirschner wires.



A.

B.

Fig. 2.—*A*, Fracture-dislocation at tarsometatarsal joints. *B*, After reduction and fixation with Kirschner wires.

bandage is applied to prevent subsequent edema, and use of the foot is encouraged. This method has been uniformly satisfactory, and there have been no complications.

A.

B.

Fig. 3.—*A*, Tarsometatarsal dislocations. *B*, After open reduction and fixation with Kirschner wires.

SUMMARY

It is often difficult or impossible to maintain the reduction of dislocations and fracture-dislocations of the tarsal and metatarsal bones by plaster of Paris, or by various forms of internal fixation. A simple and effective form of internal fixation for these injuries with Kirschner wires has been described.

APPENDICAL CALCULI

Incidence and Clinical Significance

Benjamin Felson, M.D., Cincinnati, Ohio

(From the Department of Radiology, University of Cincinnati College of Medicine)

IN A previous communication[1] 10 cases of appendical calculi were reported. In 9 of these the calculi were demonstrated roentgenologically and their presence was subsequently established by exploration in 8. It was further shown, in a review of 100 published cases and a study of our own material, that appendical calculi were associated with acute appendicitis in more than 90 per cent of the cases and that perforation occurred in almost 50 per cent. The diagnosis was made roentgenologically by the demonstration of one or more laminated calculi in close proximity to the gas-filled cecum, usually by means of stereoscopic anteroposterior films of the abdomen. It was concluded that appendicitis with calculus is more serious than appendicitis without calculus, and that the presence of appendical calculi is an indication for surgery.

Since the earlier study we have recognized roentgenologically 7 additional cases of appendical calculi. All of these were associated with acute appendicitis, and 6 were subsequently confirmed by operation.

Impressed by the frequency with which this condition is encountered among the relatively few cases of acute appendicitis with preoperative x-ray examinations, it appeared advisable to investigate the actual incidence of calculi in acutely diseased and normal appendices.

MATERIAL

Seventy-five acutely inflamed appendices and 183 normal appendices were radiographed for the presence of calculi. These were collected serially without selection. The former were all surgical specimens; the latter were obtained from autopsy (160 specimens) and from surgery (23 specimens). The normal surgical specimens had been removed incidentally during abdominal operations for other conditions.

RESULTS

Table I shows that appendical calculi were encountered in 33.3 per cent of the acutely inflamed appendices but were seen in only 2.7 per cent of the normal specimens. In the latter group, calculi were found only in the autopsy material. Appendical calculi, therefore, occurred more than ten times as often in acutely diseased appendices as in normal appendices.

The calculi were graded with respect to their roentgenographic size and density in an effort to determine whether they might have been visible on a plain film of the abdomen, had one been made. In at least 9 of the 25 cases of acute appendicitis, the calculi would almost certainly have been visible on an abdominal film of good quality (Fig. 1). In 2 of the 5 normal appendices, the

Received for publication, Aug. 10, 1948.

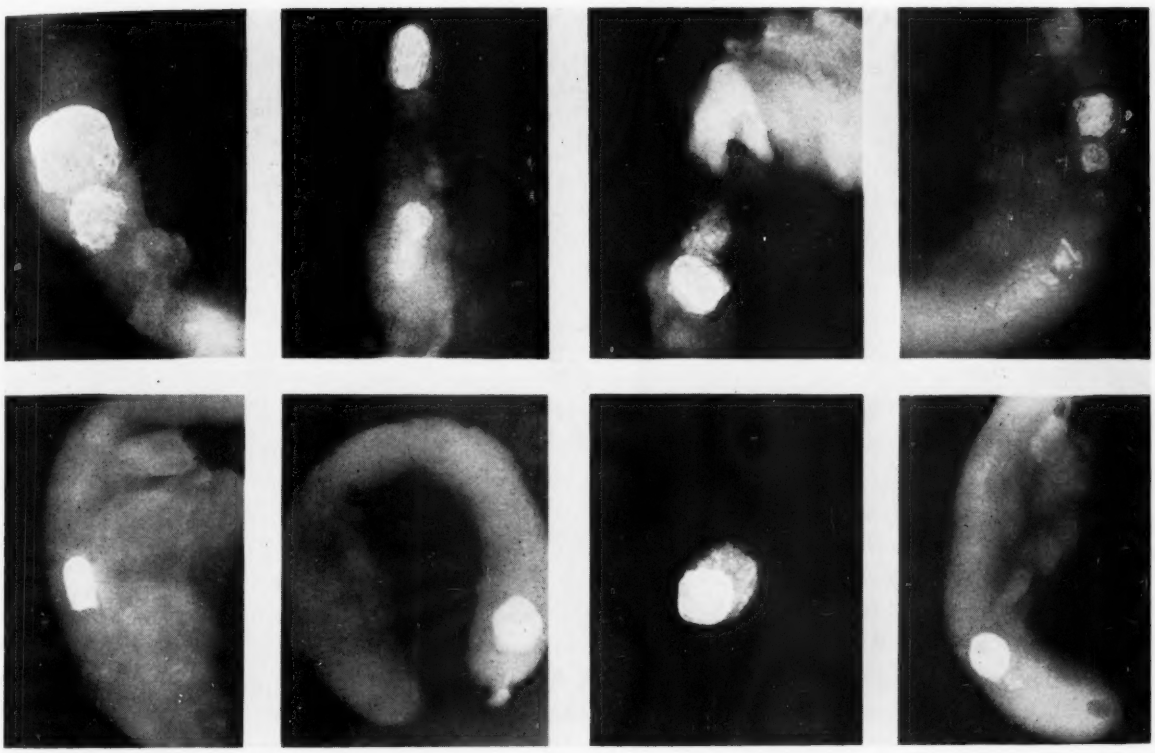


Fig. 1.—Roentgenograms of acutely diseased appendices containing calculi.

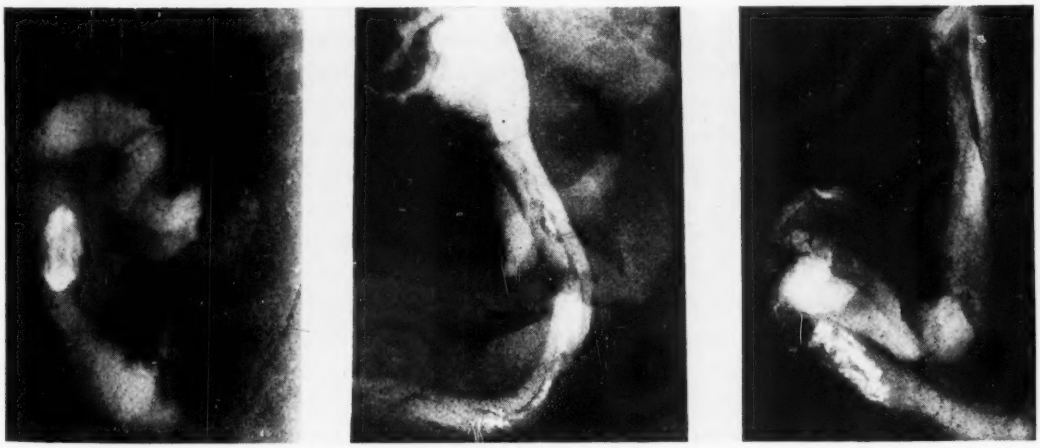


Fig. 2.—Roentgenograms of normal appendices containing calculi. In two additional cases the small size of the calculi precluded satisfactory photographic reproduction.

TABLE I

	NO. OF CASES	CALCULI PRESENT
Acute appendicitis	75	25 (33.3%)
Normal appendix	183	5 (2.7%)

calculi might have been detected on an abdominal film (Fig. 2). It might have been possible, therefore, to demonstrate calculi on abdominal films in at least 9 of the 75 cases (12 per cent) of acute appendicitis and in 2 of the 183 cases (1 per cent) with normal appendices.

Although the number of cases is admittedly small, it is of interest to note in Table II that perforation occurred in 36 per cent of the 25 cases of acute appendicitis witih calculi, but in only 12 per cent of the 50 cases without calculi.

TABLE II

	CASES	PERFORATION
Acute appendicitis with calculi	25	9 (36%)
Acute appendicitis without calculi	50	6 (12%)

DISCUSSION

Hellmer (quoted by Steinert and co-workers[6]) found appendical calculi in 15 per cent of 45 cases of acute appendicitis, Kadrnka and Bardet[2] in 3.8 per cent of 180 cases, and Steinert and co-workers[6] in 9.6 per cent of 104 cases. These figures are based on preoperative films. As far as can be determined, no studies made on roentgenograms of anatomic specimens have hitherto been recorded.*

It is apparent from this study that appendical calculi are of relatively common occurrence. Nevertheless, many experienced surgeons state that they have rarely encountered *calcified* appendical fecaliths although soft fecal masses have been observed frequently. This paradox was explained in a number of the author's specimens in which considerable calcification was demonstrated on the films but could not be palpated. Although many soft inspissated fecal masses are radiolucent, a significant number do contain radiopaque calcium without an increase in consistency. Of 30 cases reviewed in a previous article,[1] the fecaliths were hard in 22 and soft in 8.

From this study there would appear to be a correlation between the occurrence of appendical calculi and the development of acute appendicitis. The clinical material substantiates this relationship. Of 15 patients with appendical calculi demonstrated on preoperative abdominal films, 13 had acute appendicitis. One, although symptom-free, had had a previous perforation of the appendix. In only one instance was there no evidence of appendical disease. Kleeblatt[3] and Shelley[5] each reported upon such patients in whom acute appendicitis subsequently developed.

Since many patients with appendical calculi fail to give a history of previous attacks, it appears likely that calculi, at least in some cases, represent

*Since this manuscript was submitted, a study based on roentgenograms of surgical specimens was encountered in an article on appendicitis by Bowers.[9] He came to similar conclusions and cited comparable studies by several other authors.

the cause rather than the result of acute inflammation. Obstruction of the appendical lumen by the calculus undoubtedly plays a role in the production of the inflammatory process.[8] In support of this viewpoint, it was found that in no case in which the relative locations were recorded did the perforation occur proximal to the calculus.

The relatively high incidence of perforation in this material appears well documented in the reports of other authors.[6, 7, 9] Perforation is said to occur earlier when calculi are present,[4] but no attempt has been made to study this point. Similarly, no attempt has been made to correlate the clinical findings, since, at the present time, roentgen methods appear to offer the sole means of diagnosis of appendical calculi.

SUMMARY AND CONCLUSIONS

Radiographs of appendices removed surgically and at autopsy were made to determine the presence of appendical calculi. Calculi were found in 33.3 per cent of specimens with acute appendicitis and in only 2.7 per cent of appendices without disease. Perforation occurred three times as often in acute appendicitis with calculi as in acute noncalculus appendicitis.

From this and previous studies it would appear that a large majority of patients with roentgenographically demonstrable appendical calculi have acute appendicitis, and that among these the incidence of perforation is unusually high. It is apparent that the presence of calculi in the appendix, though relatively common, is nonetheless of serious import, and the need for early recognition is obvious.

The recognition of appendical calculi can be made preoperatively only by means of roentgen study. The demonstration of a laminated calculus in the right lower quadrant in close proximity to the gas-filled cecum may be taken as presumptive evidence of appendical stone. If, in addition, the patient has acute lower abdominal symptoms, the diagnosis of acute appendicitis is almost certain.

It follows that the demonstration of an appendical calculus in an acute abdomen is a major indication for immediate surgical intervention.[8] Even in the absence of acute symptoms, appendectomy would still seem indicated, in view of the possibility that acute appendicitis with perforation may supervene.

The author is indebted to Drs. Edward A. Gall, Philip Wasserman, Edward C. Elsey, and Daniel F. Richfield for their assistance in this study.

REFERENCES

1. Felson, B., and Bernhard, C. M.: The Roentgenologic Diagnosis of Appendiceal Calculi, Radiology **49**: 178-191, 1947.
2. Kadrnka, S., and Bardet, P.: L' appendicite calculeuse, J. de radiol. et d' electrol. **18**: 515-530, 1934.
3. Kleeblatt, F.: Appendixsteine im Röntgenbild, München. med. Wchnschr. **67**: 1289, 1920.
4. Murphy, J. B.: Appendiceal Concretion Producing Ulceration, Perforation and Acute Peritonitis, S. Clin. North America **4**: 28-33, 1915.
5. Shelley, H. L.: Calcified Fecalith in the Appendix, SURGERY **3**: 658-662, 1938.
6. Steinert, R., Hariede, I., and Christiansen, T.: Roentgenologic Examination of Acute Appendicitis, Acta radiol. **24**: 13-37, 1943.
7. Thomas, S. F.: Appendiceal Coproliths, Radiology **49**: 39-49, 1947.
8. Wangensteen, O. H., and Bowers, W. F.: Significance of the Obstructive Factor in the Genesis of Acute Appendicitis, Arch. Surg. **34**: 496-526, 1937.
9. Bowers, W. F.: Appendicitis, Arch. Surg. **39**: 362-422, 1939.

GELATIN SPONGE IN CARDIAC VALVULOTOMY

Report of Two Cases

J. Manly Stallworth, M.D., and Horace G. Smithy, M.D.
Charleston, S. C.

(From the Department of Surgery, Medical College of the State of South Carolina and Roper Hospital)

THE operation of aortic valvulotomy in experimental animals[1, 2] and certain considerations in the surgical treatment of human subjects with mitral stenosis[3] have been presented previously. The procedure is intended to increase the size of the mitral or aortic orifice by removing a segment of the stenosed valve.

Eight patients have been operated upon for mitral stenosis due to rheumatic heart disease. There were two deaths, one ten hours postoperatively and the other three days after operation. Detailed observations on these cases will be reported subsequently. During the operation on two of the patients, there occurred severe hemorrhage from wounds of the auricular wall. Bleeding could not be stopped with sutures but was completely controlled by the direct application of dry, absorbable gelatin sponges to the auricular wounds. Effectiveness of the gelatin sponge, without supplementary suture, in controlling hemorrhage from wounds produced in human hearts led to the presentation of the cases reported herein.

Since Correll and Wise[4] first reported the properties of an absorbable gelatin sponge designed primarily for hemostasis, numerous contributors have established the usefulness of this agent in surgery. Pilcher and Meacham[5] and Light and Prentice[6, 7] have proved this material to be a valuable addition to the group of hemostatic substances in experimental and clinical neurosurgery. Jenkins and co-workers[8, 9] found the gelatin sponge was absorbed in about five weeks in dogs and that it had a definite hemostatic action per se when applied with moderate pressure to bleeding surfaces. Later, these authors[10, 11] showed that hemorrhage following partial resection of the dog liver could be controlled in three to ten minutes with a minimal loss of blood. Supplementary suture was unnecessary. In a like manner it was found that a "patch" of gelatin sponge placed over experimental wounds of the large veins, including the vena cava,[10] adequately controlled bleeding. Massive hemorrhage following through-and-through wounds of the aorta[11] in dogs was controlled in fifteen of seventeen animals by wrapping the vessel with dry, compressed gelatin sponges supported by a chromic catgut sheath which was held in place by several sutures of catgut around the sheath. Smithy, Parker, Pratt-Thomas, and Deyerle[1, 2] demonstrated the effectiveness of gelatin sponges supported by sutures in the periaortic areolar tissue in the closure of aortic wounds in experimental aortic valvulotomy. Jenkins and his associates[12-14] pointed out that relatively large wounds in the

Received for publication, Aug. 16, 1948.

auricles and ventricles of dogs could be closed without primary or secondary hemorrhage in practically all the wounds by a "patch" of dry compressed gelatin sponge held in place from three to thirteen minutes and supported by partial closure of the pedicardium. Supplementary suture was necessary for complete hemostasis in two of the eighteen animals with auricular wounds; none was required in the ventricular wounds. Further refinements in technique and the clinical application of gelatin sponges have been described.[15, 16]

CASE REPORTS

CASE 1 (Roper Hospital No. 67739).—A 39-year-old white woman was admitted to the hospital April 17, 1948, with a history of rheumatic fever at the age of 9 years and presenting classical signs of mitral stenosis. She had been in congestive heart failure three times and on admission, though free of signs of heart failure, had rather marked dyspnea and a feeling of substernal constriction on exertion. Because of the severity of these symptoms she had been forced to give up her job as laboratory technician and greatly restrict her household tasks. Venous pressure reading in the median vein of the forearm was 100 mm. of water. The circulation time, arm-to-tongue, using magnesium sulfate was 15 seconds. Roentgenograms of the chest, including oral barium, showed enlargement of the left atrium. Electrocardiographic impression was slight right axis deviation and probable auricular hypertrophy. Routine laboratory studies were normal.

On April 20, 1948, a cardiotomy was performed under endotracheal inhalation anesthesia. The approach was through the left anterior chest wall with excision of the second, third, and fourth costal cartilages. After the pleura was entered through the third intercostal space, the pericardium was opened with a vertical incision about 1 cm. anterior to the phrenic nerve. The pericardial fluid was normal in appearance and not increased in amount. The heart was then bathed in 15 c.c. of 2 per cent procaine applied topically and allowed to pool in the pericardial sac. The wall of the auricular appendage was infiltrated with 5 c.c. of 1 per cent procaine.[3] After a fine catgut purse-string suture had been placed in the infiltrated portion of the auricular appendage, the latter was opened to admit a specially devised biting valvulotome. Much difficulty was encountered in entering the mitral orifice with the instrument. During the manipulation, the instrument was accidentally forced through the wall of the auricle posteriorly near the coronary sulcus so as to protrude into the pericardial cavity, producing a wound which was inaccessible to suture. Hemorrhage from the traumatic opening was controlled by digital presure while a segment from the margin of the stenotic mitral orifice was removed. After the instrument had been withdrawn from the heart and the wound in the appendage repaired, a dry absorbable gelatin sponge measuring 10 by 7.5 cm. was placed against the posterior auricular tear and held in position with slight digital pressure until the sponge was saturated with blood. Carefully the pressure was released and the pericardium over the auricle posteriorly was held taut until sutures approximating the superior portion of the pericardial incision could be secured, thus maintaining constant snug support to the gelatin sponge. There was no further hemorrhage from the wound. The inferior portion of the pericardial sac was not closed. There were no arrhythmias during the operation.

After the patient was returned to her room and while receiving blood intravenously, the blood pressure dropped to 40/20; however, with increased rate in the flow of blood and supportive treatment, there was satisfactory response and the blood pressure remained well above shock level. During the first twenty-four hours, serosanguineous drainage from an intercostal catheter amounted to 550 c.c. and during the second twenty-four hours the catheter output was 100 c.c., indicating no gross bleeding from the heart operation.

Electrocardiographs made two days after the operation showed occasional auricular extrasystoles. The venous pressure and circulation time were essentially unchanged. On the third day the intercostal drainage system no longer showed free exchange and the catheter was removed after examination revealed no appreciable fluid or air in the pleural cavity.

X-ray examination of the chest ten days after operation showed moderate generalized increase in heart size (13.5 cm. compared to 12 cm. preoperatively in transverse diameter), a small, loculated area of pleural effusion at the level of the fourth rib anteriorly, and a small amount of fluid at the costophrenic angle. A thoracentesis in the ninth interspace posteriorly yielded 150 c.c. of serosanguineous fluid.

Except for troublesome nausea during the first few days postoperatively, the course was entirely satisfactory. The patient was allowed out of bed on the fifth day after operation and thereafter increased her activity gradually. She no longer complained of the pounding heart action, substernal constriction, cough, orthopnea, or lethargy which were present before the operation and was able to be active with less dyspnea. She was discharged from the hospital May 7, 1948, eighteen days after admission, in good condition.

The patient in a communication in June, 1948, stated that she was then able to drive a car in heavy traffic, carry out ordinary household tasks, and enjoy downtown shopping. In July, 1948, she resumed her work as a laboratory technician on a part-time basis and had no return of the original complaints.

CASE 2 (Roper Hospital No. 68326).—A 36-year-old white woman was admitted to the hospital May 13, 1948, for cardiac evaluation. She gave a history of rheumatic fever at the age of 8 years but experienced no serious effects until 1942, when she developed dyspnea on exertion and frequent palpitation. These symptoms slowly progressed, as did orthopnea, dependent edema, and mild hemoptysis during the past year.

Examination revealed typical mitral stenosis with moderate congestive heart failure. Venous pressure readings varied between 90 and 95 mm. of water in the median vein of the forearm, and the circulation time was 16 seconds. Urinalysis and blood count were normal. Urea nitrogen was 12 mg. and vital capacity 1,800 c.c. Roentgenograms of the chest after oral barium showed a prominent left auricle, borderline cardiomegaly, and hypertrophic arthritis of the thoracic vertebrae. No abnormalities except occasional auricular extrasystoles were seen on the electrocardiograph.

The congestive heart failure improved with bed rest and increased digitalis dosage. The patient complained of pain over the precordium, which was believed to be caused by arthritis of the upper thoracic vertebrae. Complete relief was afforded by intercostal nerve block with eucupin-in-oil.

On May 26 a cardiotomy was attempted through an anterior thoracic incision after reflection of the breast upward, resection of the third rib to the mid-axillary line, and removal of the second and fourth costal cartilages. The pericardial fluid was clear and normal in amount. The heart and pulmonary artery were slightly enlarged and the left auricle was extremely dilated and tense. Fifteen cubic centimeters of 2 per cent procaine were applied topically over the surface of the heart and a purse-string suture of catgut was placed in the auricular appendage preparatory to opening the left auricle. The latter was found to be extremely thin and friable and the purse string immediately tore out, resulting in severe hemorrhage. Several attempts at controlling the bleeding by suture proved fruitless, the hemorrhage simply increasing with each successive attempt at closure of the defect. The entire appendage was enveloped in an absorbable gelatin sponge which was made secure by suturing the cut surfaces of the pericardium overlying the auricle. This provided firm, tamponading pressure of the appendage against the pulmonary conus and prevented movement of the gelatin pack. Thus, hemorrhage was effectively controlled. However, it was felt that the patient's general condition was such as to contraindicate further attempt at entering the heart. There were no serious arrhythmias during the procedure. A catheter was inserted through the ninth interspace posterolaterally and the chest was closed in layers with interrupted silk sutures.

Upon the patient's return to her room, blood pressure was well above shock level and remained so throughout the postoperative course. Intercostal catheter drainage amounted to 250 c.c. of bloody fluid during the first twenty-four hours and 350 c.c. during the next forty-eight hours. Clinically, there were occasional paroxysms of fibrillation. Electro-

cardiographs taken at intervals showed the following results: first postoperative day, normal sinus rhythm; second postoperative day, impure auricular flutter; sixth postoperative day, sinus rhythm normal, but there was first degree auriculoventricular block; seventeenth postoperative day, normal sinus rhythm with auriculoventricular delay.

The patient sat up on the fourth postoperative day and gradually increased her activity thereafter. The chest wound healed per primam and there were no significant changes in the cardiac complaints or findings other than those recorded here.

Nineteen days after operation, the original chest incision was reopened after excision of the scar and the breast was reflected upward in the usual manner. Subperiosteal resection of the fifth rib from the sternum to the anterior axillary line was carried out along with division of the sixth costal cartilage. The thorax was entered through the bed of the fifth rib. There were many friable adhesions binding the left lung to the parietal pleura and to the pericardium. The left pleural cavity contained approximately 200 c.c. of clear serous fluid. The left auricular appendage was enveloped by adhesions consisting of the pericardium and the upper lobe of the lung at the site where the gelatin sponge had been placed previously. The pericardium itself was adherent to the epicardial surface of the heart by flimsy adhesions. As noted at the first operation, the pulmonary conus was dilated and very tense to palpation. After the adherent pericardium was freed, the heart was delivered into the operative wound by manual displacement. Over its surface was poured about 15 c.c. of 2 per cent procaine. Numerous arrhythmias occurred despite the topical application of procaine, a finding noted in our experimental studies.[3] A relatively avascular area of the wall of the left ventricle near its apex was infiltrated with 10 c.c. of 1 per cent procaine solution. Into the infiltrated area was placed a purse-string suture of chromic catgut. No arrhythmias occurred during this procedure. The heart was opened within the confines of the purse-string suture and the valvulotome introduced into the left ventricular chamber. By manipulation, the instrument was inserted through the thickened and narrowed mitral valve whereupon it was impinged upon the anterior margin of the stenotic orifice. A segment of tissue measuring 1 cm. in length was excised from the thickened valvular margin. During the course of the actual valvular excision, numerous ventricular extrasystoles occurred but disappeared upon the withdrawal of the valvulotome. The purse-string suture was tied, closing the opening in the ventricular wall, and was reinforced with interrupted silk sutures. A marked decrease in the tension of the pulmonary conus was noted. The chest was closed in layers after drainage by an intercostal catheter.

Postoperatively the patient's condition was good. Approximately 450 c.c. of bloody serous fluid escaped through the intercostal catheter during the first twenty-four hours. Two subsequent thoracenteses yielded a total of 420 c.c. Electrocardiograph on the first postoperative day showed depressed diphasic T wave suggesting digitalis effect. On the eighth postoperative day the tracings revealed normal sinus rhythm. The shape of S-T_1 and S-T_2 resembled somewhat an anterior myocardial infarct, a finding noted in our earlier experimental studies.[2] Stethogram showed a presystolic murmur and no stethographic evidence of systolic murmur. Venous pressure reading in the cubital vein was 90 mm. of water one day after operation. This was repeated on the eighth postoperative day and found to be 80 mm.

The prominent preoperative symptoms of cough with occasional hemoptysis, dyspnea on exertion, orthopnea, severe palpitation, and edema of the ankles completely disappeared. Mercurial diuretics were no longer necessary. The patient was discharged on June 26, 1948 (twelve days postoperatively), in good condition. About one month after the patient's discharge from the hospital, her physician stated in a letter that the patient's murmur was barely audible, heart action much less labored, and there was no evidence of cardiac embarrassment on exertion.

COMMENT

The hemostatic action of dry gelatin sponge in the control of hemorrhage from wounds of the auricle in the two cases presented demonstrates the effectiveness of this material as an adjunct in surgery of the heart.

In the reports of Elkin,[17-20] Beck,[21, 22] Bigger,[23-25] Griswold and Maguire,[26, 27] Linder and Hodo,[28] Blalock and Ravitch,[29] and Maguire,[30] the treatment of traumatic wounds of the heart has been thoroughly discussed. The control of hemorrhage from these wounds has always been a problem, especially in areas inaccessible to suture or those adjacent to coronary vessels. The use of gelatin sponge as a supplement to suture in controlling hemorrhage from stab wounds of the heart has been reported by Brown (two cases)[31] and Maguire and Griswold (one case).[27]

The wound of the left auricle in Case 1 represents a type which cannot be approached by suture, and control of bleeding would have been impossible without an absorbable hemostatic agent. In Case 2, the wounds were readily accessible, but the dilated, thin, friable wall of the auricle would not support the purse string suture placed in preparation for cardiotomy. Here again hemostasis could be established only through a nonsuture method. During the second operation in Case 2, the auricular appendage was inspected and the gelatin sponge which had been applied nineteen days earlier was found firmly adherent to auricle and adjacent pericardium with no evidence of secondary hemorrhage. It is significant that only a transient arrhythmia of minor degree occurred in one of the patients postoperatively despite the large amount of gelatin sponge in contact with the auricles.

The outcome of these cases is clinical corroboration of the experimental work on absorbable gelatin sponge by Jenkins and his associates,[12, 13, 14] who have demonstrated the effectiveness of gelatin sponge in the repair of wounds of the heart in dogs.

SUMMARY

Case reports are presented of two patients having mitral stenosis who were subjected to mitral valvulotomy. In each case severe hemorrhage from a wound of the left auricle was effectively controlled by the use of absorbable gelatin sponge without supplementary suture.

Each patient recovered uneventfully from the operation and is leading a more normal life than was possible preoperatively.

REFERENCES

1. Smithy, H. G., and Parker, E. F.: Experimental Aortic Valvulotomy: A Preliminary Report, Surg., Gynec. & Obst. **84**: 625, 1947.
2. Smithy, H. G., Pratt-Thomas, H. R., and Deyerle, H. P.: Aortic Valvulotomy; Experimental Methods and Early Results, Surg., Gynec. & Obst. **86**: 513, 1948.
3. Smithy, H. G.: The Control of Arrhythmias Occurring During Operation Upon the Valves of the Heart: Experimental and Clinical Observations, South. Surgeon **14**: 611, 1948.
4. Correll, J. T., and Wise, E. C.: Certain Properties of a New Physiological Absorbable Sponge, Proc. Soc. Exper. Biol. & Med. **58**: 233, 1945.
5. Pilcher, C., and Meacham, W. F.: Absorbable Gelatin Sponge and Thrombin for Hemostasis in Neurosurgery, Surg., Gynec. & Obst. **81**: 365, 1945.
6. Light, R. U., and Prentice, H. R.: Gelatin Sponge; Surgical Investigation of a New Matrix Used in Conjunction With Thrombin in Hemostasis, Arch. Surg. **51**: 69, 1945.
7. Light, R. U., and Prentice, H. R.: Studies in Neurosurgical Hemostasis; Surgical Investigation of a New Absorbable Sponge Derived From Gelatin for Use in Hemostasis, J. Neurosurg. **5**: 435, 1945.

8. Jenkins, H. P., and Clarke, J. S.: Gelatin Sponge, A New Hemostatic Substance, Studies on Absorbability, Arch. Surg. **51**: 253, 1945.
9. Jenkins, H. P., Janda, R., and Clarke, J. S.: Clinical and Experimental Observations on the Use of Gelatin Sponge or Foam, SURGERY **20**: 124, 1946.
10. Jenkins, H. P., and Janda, R.: Studies on the Use of Gelatin Sponge or Foam as a Hemostatic Agent in Experimental Liver Resections and Injuries to Large Veins, Ann. Surg. **124**: 952, 1946.
11. Jenkins, H. P., Senz, E. H., Owen, H. W., and Jampolis, R. W.: Control of Arterial Hemorrhage by a Gelatin Sponge "Cuff" and Chromic Catgut Sheath, A New Experimental Method, Arch. Surg. **55**: 637, 1947.
12. Jenkins, H. P., Senz, E. H., Owen, H. W., and Jampolis, R. W.: Present Status of Gelatin Sponge for Control of Hemorrhage With Experimental Data on Its Use for Wounds of the Great Vessels and the Heart, J. A. M. A. **132**: 614, 1946.
13. Jampolis, R. W., Jenkins, H. P., Newman, M. M., and Nardi, G. L.: Control of Hemorrhage From the Cardiac Auricles by the Gelatin Sponge, An Experimental Study, SURGERY **22**: 198, 1947.
14. Jenkins, H. P., Owen, H., Senz, E., and Jampolis, R. W.: Control of Hemorrhage From Wounds of the Heart by the Gelatin Sponge "Patch" Technic, A New Experimental Method, Ann. Surg. **126**: 973, 1947.
15. Jenkins, H. P.: The Absorbable Hemostatic Agents, Surg., Gynec. & Obst. **83**: 403, 1946.
16. Jenkins, H. P.: Control of Hemorrhage by Gelatin Sponge, J. Internat. Coll. Surgeons **10**: 521, 1947.
17. Elkin, D. C.: Wounds of the Heart, Ann. Surg. **120**: 817, 1944.
18. Elkin, D. C.: Diagnosis and Treatment of Cardiac Trauma, Ann. Surg. **114**: 169, 1941.
19. Elkin, D. C.: The Diagnosis and Treatment of Wounds of the Heart, J. A. M. A. **111**: 1750, 1938.
20. Elkin, D. C.: Suturing Wounds of the Heart, Ann. Surg. **95**: 573, 1932.
21. Beck, C. S.: Further Observations on Stab Wounds of the Heart, Ann. Surg. **115**: 698, 1942.
22. Beck, C. S.: Wounds of the Heart, Technique of Suture, Arch. Surg. **13**: 205, 1926.
23. Bigger, I. A.: Diagnosis and Treatment of Heart Wounds: Summary of 25 Cases, South. M. J. **33**: 6, 1940.
24. Bigger, I. A.: Heart Wounds, A Report of 17 Patients Operated Upon in the Medical College of Virginia, J. Thoracic Surg. **8**: 239, 1939.
25. Bigger, I. A.: Wounds of the Heart and Pericardium, South. M. J. **25**: 785, 1932.
26. Griswold, R. A., and Maguire, C. H.: Penetrating Wounds of the Heart and Pericardium, Surg., Gynec. & Obst. **74**: 406, 1942.
27. Maguire, C. H., and Griswold, R. A.: Further Observations on Penetrating Wounds of the Heart and Pericardium, Am. J. Surg. **74**: 721, 1947.
28. Linder, H., and Hodo, H.: Stab Wounds of the Heart and Pericardium, South. M. J. **37**: 261, 1944.
29. Blalock, A., and Ravitch, M. M.: A Consideration of the Nonoperative Treatment of Cardiac Tamponade Resulting From Wounds of the Heart, SURGERY **14**: 157, 1943.
30. Maguire, D. L.: Penetrating Wounds of the Heart, South. Med. & Surg. **106**: 411, 1944.
31. Brown, A. G.: Wounds of the Heart With Case Reports, J. South Carolina M. A. **43**: 127, 1947.

Case Reports

HEMANGIOMA OF THE LIVER

Report of a Case

John G. Riddler, M.D.,* New Orleans, La., and
Gordon F. Madding, M.D., San Angelo, Texas

CAVERNOUS hemangioma of the liver occurs infrequently but, when encountered, the diagnosis and surgical management offer a real problem. Shumacker in a thorough review of the literature in 1941 was able to find only 67 cases of benign hemangioma of the liver in which operation had been performed. Since then there have been 4 additional reports. Morton resected a large, pedunculated, cavernous hemangioma which originated in the liver. Ayres Netto and Amorim reported removal of the entire left lobe of the liver to which a hemangioma was attached. Pickrell and Clay described a cavernous hemangioma of the left lobe of the liver which was satisfactorily removed by lobectomy. Peale and Coombs were able to extirpate a hemangioma of the liver measuring 8 cm. in diameter, which was attached by a broad base to the fissure between the right and left lobes. We recently discovered a large cavernous hemangioma of the liver during a laparotomy and believe that it should be added to the growing list of reported cases. This case is also of interest because, as far as we have been able to determine, it is the first instance in which bleeding from a hemangioma of the liver has been controlled by the use of gel foam. Our case brings the total number of recorded cases to 72.

CASE REPORT

J. C. M., a 60-year-old white married woman, was admitted to the Shannon West Texas Memorial Hospital, Jan. 25, 1947, because of high blood pressure, "spitting up" of food, and an enlarged liver. In 1932 she was told her blood pressure was over 200, and during the past five years she had noticed a frontal headache and "spots in front of her eyes" when the systolic pressure exceeded this level. Eructation of food had been occurring for ten to twelve years and seemed to follow ingestion of considerable amounts of food. For the past six months she had experienced a feeling of fullness in the abdomen, most noticeable when she sat down or bent forward. The only abnormality on physical examination elsewhere in 1944 was hypertension. In October, 1946, a cholecystogram done in another city revealed a normal gall bladder but an enlarged liver. In December, 1946, she consulted Dr. F. T. McIntire in regard to the high blood pressure and hepatomegaly and she was seen by us in consultation.

The only significant physical findings on admission were: blood pressure, 190 systolic, 128 diastolic; old, low midline scar from a previous panhysterectomy; and a mass in the right side of the abdomen. The tumor seemed to originate from the entire inferior surface of the right lobe of the liver. It extended medially to the midline, laterally as

Received for publication, Aug. 6, 1948.
*Fellow in Surgery, Alton Ochsner Medical Foundation, New Orleans, La.

far as the right anterior axillary line, and downward to the level of the iliac crest. Its consistency was moderately firm and no nodules could be outlined. Auscultation over the tumor revealed no bruit.

Results of laboratory studies were as follows: normal serologic reactions, normal urine, hemoglobin 87 per cent, red blood count 4,390,000, white blood count 6,000 with a normal differential count, and nonprotein nitrogen 30 mg. per cent. Intravenous pyelography disclosed slight downward displacement of the right kidney by a mass in the upper quadrant which was believed to be liver. A roentgenogram of the chest showed moderate cardiac enlargement and normal pulmonary fields. An electrocardiogram was essentially normal. The sodium amytal sedation test for hypertension resulted in a drop in blood pressure to 124 systolic and 68 diastolic and it was thought at this time that the patient should have a thoracolumbar sympathectomy at a later date.

Abdominal exploration was decided upon in order to determine the exact nature of the abdominal mass. The preoperative diagnosis was tumor of the liver, type unknown.

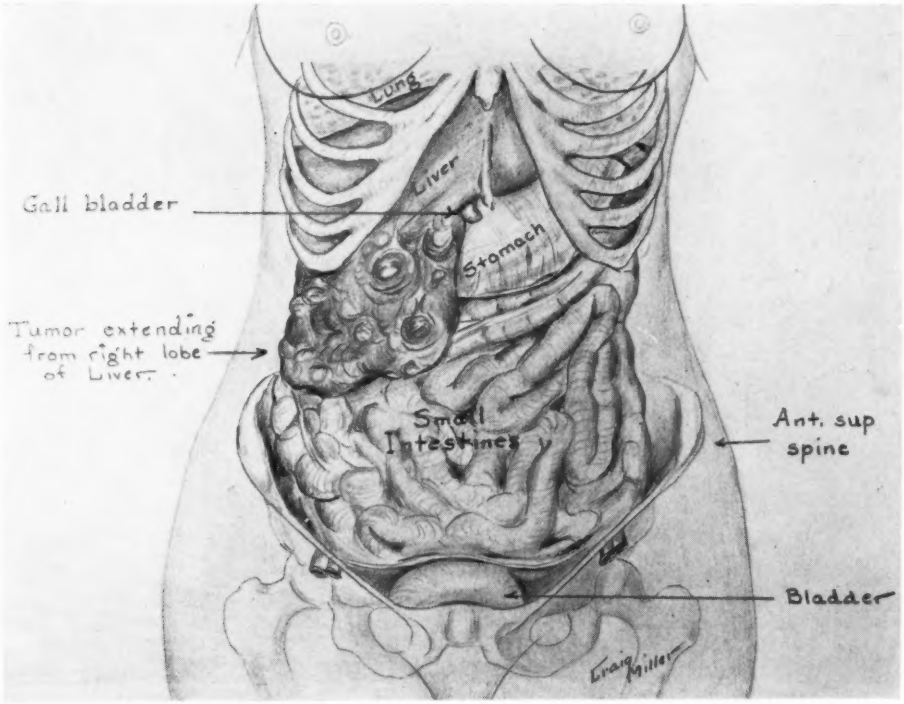


Fig. 1.—Drawing indicating size of the tumor and relationship to adjacent viscera.

Exploratory laparotomy was performed by one of us (G. F. M.) on Jan. 31, 1947. Under endotracheal ether anesthesia a right rectus incision was made, the peritoneum opened, and the viscera were inspected. A large tumor which originated from the right lobe of the liver and extended downward to the level of the iliac crest was encountered (Fig. 1). It was purplish-red and projecting from its surface were slightly raised nodules varying from 1 to 6 cm. in diameter. It was spongy and rather easily compressible. Pressure applied to a nodule caused an indentation which slowly disappeared when the pressure was released. A fine needle was inserted into the tumor and blood was freely aspirated. A specimen, approximately 1 by 1 by 2 cm., was taken from one of the larger nodules for biopsy. Blood oozed freely from this site and the cut surfaces disclosed blood-filled channels separated by trabeculae. The cut edges of the defect were approximated with catgut mattress sutures but bleeding continued from between the margins of the

wound as well as from the needle holes. A piece of gel foam moistened in thrombin was then applied and all bleeding ceased. A specimen for biopsy was taken from the right lobe of the liver above the tumor and hemostasis was effected by filling the defect with gel foam which had been immersed in saline solution. Although extirpation of this hemangioma would have been the ideal procedure, it was considered inadvisable because of the tumor's large area of attachment to the liver. The abdomen was closed in layers. The patient's condition was satisfactory at the completion of the operation. There was no evidence of postoperative bleeding and recovery was uneventful.

Microscopic studies showed the tumor to be a cavernous hemangioma (Fig. 2). There were large, blood-filled sinuses which were lined by endothelial cells. Between these vascular spaces were moderately wide fibrous trabeculae. There was no evidence of malignant change in either the endothelial component or in the fibrous framework. Microscopic examination of the normal liver adjacent to the tumor showed no scarring.

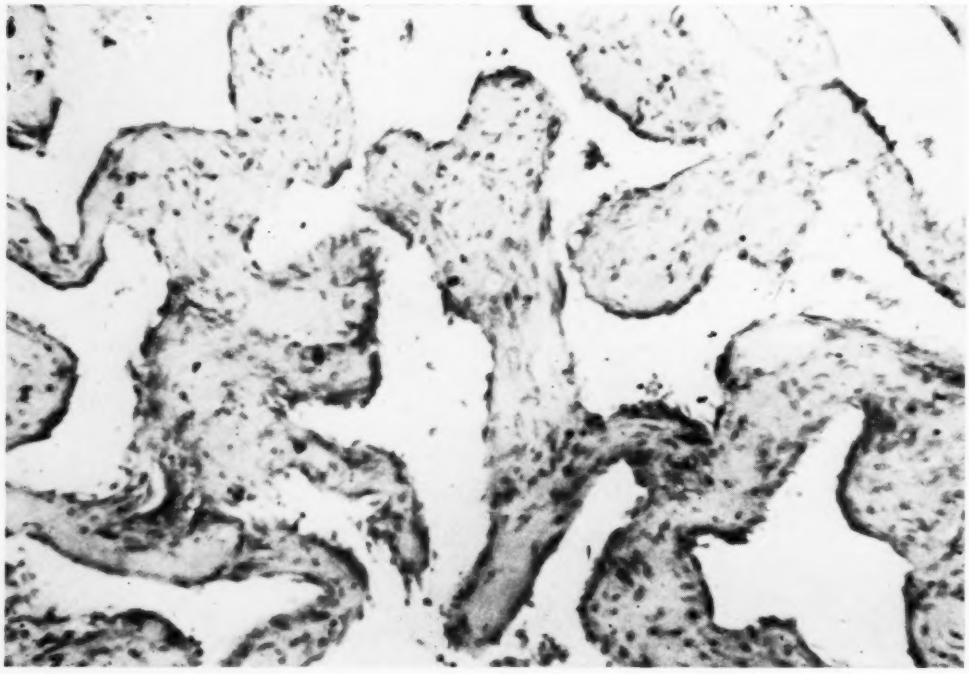


Fig. 2.—Photomicrograph showing blood containing channels separated by connective tissue trabeculae.

On the twenty-first postoperative day roentgen therapy was instituted. From Feb. 14, 1947, to June 19, 1947, the patient received 6,860 R to the tumor through three ports—anterior, lateral, and posterior (factors: 200 kv.; 50 cm. F.S.D.; Thoreus filter). Three months after operation the unpleasant eructations had disappeared and the patient said she felt definitely better than before operation. The tumor was easily palpable but definitely reduced in size.

In October, 1947, eight months after operation, the patient had no digestive complaints and the feeling of fullness in the abdomen had definitely decreased. Examination of the abdomen showed a 50 per cent reduction in the size of the tumor. On October 17 and 27 a thoracolumbar sympathectomy was done with removal of the major, minor, and least splanchnic nerves on each side and the sympathetic ganglia and intervening trunks from the eighth dorsal to the second lumbar inclusive.

In June, 1948, seventeen months after laparotomy, abdominal examination revealed the tumor to extend below the costal margin for a distance of 5 cm. The patient had no epigastric discomfort. At this time the systolic pressure in the supine position was 200

and the diastolic pressure was 110. In the erect position the pressure was 140 systolic and 90 diastolic, but it dropped to shock level in a few seconds if she stood perfectly still. Hypotension could be avoided by moving when standing or by wearing an abdominal binder and elastic stockings.

DISCUSSION

The characteristics of this case and the ones reported by Ayres Netto and Amorim, Morton and Pickrell and Clay are typical of the general picture of cavernous hemangioma of the liver described by Shumacker in that: (1) These tumors occur more frequently in women past middle age; (2) the common initial complaints are a feeling of pressure in the abdomen and belching; (3) there is a palpable tumor in the upper abdomen; (4) the correct preoperative diagnosis is rarely made; (5) the tumors are large, purplish, soft and well demarcated from surrounding liver; (6) profuse bleeding is encountered if aspiration or biopsy of the tumor is performed; (7) resection is usually possible; and (8) convalescence is usually uneventful.

Attention has been repeatedly called to the fact that if resection is impossible, neither aspiration nor biopsy should be done because of profuse bleeding. In one of the earliest reports of hemangioma of the liver, Leech (as quoted by Mantle) used a fine aspirating needle, and bleeding, which was uncontrollable, resulted in death of the patient. M'Weeney encountered severe hemorrhage after incising a hemangioma. His patient rallied from the operation but died one week later following hematemesis. The cause of death was not determined by autopsy. In our case both aspiration and biopsy were done, and although free bleeding ensued, prompt hemostasis was obtained with gel foam, thrombin, and mattress sutures. The use of gel foam has been frequently advocated to control bleeding from the liver. Jenkins, Janda, and Clarke were successful in controlling bleeding from liver biopsy sites by the use of gel foam. Bailey and associates found gel foam to be an effective hemostatic agent in wounds of the liver and to cause much less tissue reaction than muscle. Jenkins and Janda used gel foam soaked in saline solution in hepatic resections in dogs and found it to be an effective means of controlling bleeding. As far as we can determine from the literature, our case is the first one in which gel foam has been used to control bleeding from a hemangioma of the liver.

The case under discussion is also interesting because of the effective response of this tumor to roentgen therapy. Ray reported a case of hemangioma of the liver in which resection was impossible but roentgen therapy caused considerable decrease in the size of the tumor. His patient received 10,374 R over a period of fifteen months and it was estimated that the tumor was about one-sixth of its original volume five years after operation. Morris reported a case of removal of a large hemangioma from the left lobe of the liver but a smaller hemangioma on the right lobe was permitted to remain. One month after the patient was discharged from the hospital, a mass the size of a fist appeared in the right upper part of the abdomen and was believed to represent the former small hemangioma. The patient received eight treat-

ments in one-third erythema doses and no tumor was palpable on follow-up examination. Our patient received slightly less than 7000 R over a period of four months. Eight months after operation the tumor was about one-half its original size, and seventeen months after operation it was one-third to one-fourth its original size.

SUMMARY

1. A case of benign hemangioma of the liver discovered during laparotomy is reported and the literature on this subject is brought up to date.

2. Resection of the tumor was impossible but response to roentgen therapy was satisfactory.

3. Aspiration and biopsy of benign cavernous hemangioma of the liver are no longer hazardous procedures if gel foam is used as a hemostatic agent.

REFERENCES

1. Ayres Netto, P., and Amorim, J.: Hemangioma cavernoso do lobo esquerdo do figado, Rev. de cir. de São Paulo **8**: 257-272, 1942.
2. Bailey, O. T., Ingraham, F. D., Swenson, O., Lowrey, J. J., and Bering, E. A., Jr.: Human Fibrin Foam With Thrombin as a Hemostatic Agent in General Surgery: Experimental Studies and Clinical Use, SURGERY **18**: 347-369, 1947.
3. Jenkins, H. P., and Janda, R.: Studies on the Use of Gelatin Sponge or Foam as an Hemostatic Agent in Experimental Liver Resections and Injuries to Large Veins, Ann. Surg. **124**: 952-961, 1946.
4. Jenkins, H. P., Janda, R., and Clarke, J.: Clinical and Experimental Observations on the Use of Gelatin Sponge or Foam, SURGERY **20**: 124-132, 1946.
5. Mantle, A.: An Unusually Large Angeioma of the Liver, Brit. M. J. **1**: 365-366, 1903.
6. Morris, J. H.: Hemangioma of the Liver; Successful Resection of Left Lobe, Ann. Surg. **111**: 147-150, 1940.
7. Morton, H. B.: Large Pedunculated Cavernous Hemangioma of Liver; Case Report, Am. J. Surg. **56**: 673-675, 1942.
8. M'Weeney, E. J.: Enormous Angeioma of the Liver, J. Path. & Bact. **16**: 401-403, 1912 (Proceedings, Jan. 5-6, 1912).
9. Peale, A. R., and Coombs, J. N.: A Large Hemangioma of the Liver, Successfully Removed Surgically, Am. J. Clin. Path. **16**: 792-795, 1946.
10. Pickrell, K. L., and Clay, R. C.: Lobectomy of Liver; Report of 3 Cases, Arch. Surg. **48**: 267-277, 1944.
11. Ray, B. S.: Large Cavernous Hemangioma of Liver; Report of Inoperable Case Treated With Roentgenotherapy, Ann. Surg. **109**: 373-382, 1939.
12. Shumacker, H. B., Jr.: Hemangioma of Liver; Discussion of Symptomatology and Report of Patient Treated by Operation, SURGERY **11**: 209-222, 1942.

HEMANGIOMAS OF THE ILEUM WITH INTUSSUSCEPTION

Case Report

Richard H. Weddle, M.D., and Cecil D. Snyder, M.D., Winfield, Kan.

A REVIEW of the literature relative to intussusception shows that no apparent causative factor is found in the vast majority of cases. Oberhelman and Condon[2] presented a study of 95 infants and children admitted to the Cook County Hospital between 1925 and 1945 with a diagnosis of acute intussusception. In this series, they were unable to find an initiating factor in 85 per cent. Of their patients, 68 per cent were under 1 year of age. The most frequent finding in their series was vomiting, followed in order by pain, and bloody stools. Added to these are the less frequent findings of a palpable mass and signs of intestinal obstruction.

Oberhelman and Condon considered the disease to be primarily a surgical emergency and in those requiring resection, there was a mortality rate of 42.8 per cent. There were five cases of ileo-ileal intussusception requiring resection, and their mortality rate for these was 60 per cent.

The occurrence of benign tumors of the small intestine is infrequent. Raiford[3] reported 11,500 autopsy specimens and 45,000 surgical specimens in which a total of 88 tumors of the small intestine were found; 50 of these were benign. In reporting 41 cases of benign tumor of the small bowel, at the Mayo Clinic, between the years 1907 and 1939, Weber and Kirklin[4] listed the tumors, in order of frequency, as myoma, adenoma, lipoma, fibroma, hemangioma, and osteochondroma. They were found most commonly in the duodenum, then jejunum, with the ileum occupying third place.

Lazarus and Marks,[1] in a collective review of 38 intestinal tumors of vascular origin, found most to occur solely in the small intestine; only 8 being found in the colon alone. In this group, the lesions were designated as nevi 6, angioma 11, cavernous hemangioma 11, capillary hemangioma 5, varicosities 2, cavernous phlebectasis 1, and not designated 2.

An interesting case of ileo-ileal intussusception, with a cavernous hemangioma located at the fulcrum of the intussusceptive portion of the ileum, is herewith presented.

CASE REPORT

E. B., a white male, aged 7 years, was admitted to the hospital April 30, 1948, complaining of pain in the right lower quadrant which had been present for two days. There was occasional transient pain in the epigastrium, but none associated with the periumbilical region; none in the costovertebral angles. Vomiting occurred the evening before admission to the hospital, and also on the morning of admission. The vomited material was said to have the appearance of bile and mucus. The child had had three bowel movements after the onset of pain, with no abnormalities noted in the stool. Prior to the onset of pain, he had been active, but shortly after became somewhat lethargic, with no inclination to eat, and remained quiet in bed until his hospital entrance.

Received for publication, Sept. 7, 1948.

Past History.—The child had always been rather pale, although quite active. At the age of 1 year, he had been seen in one of the university hospitals with a small mass in the region of the left axilla. This was said to have been a hemangioma. The treatment consisted of radiation to the mass, with multiple blood transfusions. He did very well following this, until the age of 6 years, when a mass re-appeared in this same area extending over the anterior portion of the upper left chest. He was re-admitted to the same hospital, and was found to be markedly anemic. He was given multiple blood transfusions, and the mass was resected, the pathologic diagnosis being hemangioma. The operative note stated that the tumor mass had apparently involved the intercostal spaces from the first to the third ribs. Other past history was not contributory, except that it was ascertained that the child had always had a poor appetite, particularly from the standpoint of protein intake.

Physical Examination.—The patient appeared extremely pale, lethargic, and undernourished. He was lying quietly in bed with the thighs flexed on the abdomen. Temperature 100° F., pulse 130, respiration 20, blood pressure 100/54. There was marked circumoral and periorbital pallor, and the nail beds appeared somewhat cyanotic. The buccal and pharyngeal mucous membranes were very pale. The posterior cervical lymph nodes were palpable. One small lymph node was palpable in the right axilla. A surgical scar, two inches in length, was present along the left lateral pectoral border. The thorax showed equal expansion, with vesicular breath sounds and a resonant percussion note throughout. The heart was minimally enlarged, extending midway between the nipple line and the anterior axillary line in the sixth left interspace. The point of maximum impulse was diffuse, heaving, and rapid. A slight systolic murmur heard both at the apex and at the base of the heart was not transmitted, and was considered to be hemic in nature. The abdomen presented point tenderness low in the right lower quadrant. There was no referred tenderness, but rebound tenderness could be elicited over the entire abdomen. There was an enlarged, tender mass occupying the right lower quadrant which was firm. Rather marked rigidity was present. Peristaltic sounds could be heard over the entire abdomen. There was no evidence of distention, and during the course of the examination, the child passed a fair amount of flatus. There was a small amount of fecal material in the rectum which showed no gross evidence of blood. Tenderness was elicited by digital examination high in the rectum, when pressure was directed toward the right lower quadrant.

Laboratory examination, on admission, showed the total red count to be 1,800,000 with 3.75 Gm. hemoglobin. The white count was 12,800 with a differential of 75 per cent segmented cells, 11 per cent stab cells, 6 per cent juvenile form, 6 per cent lymphocytes, and 2 per cent monocytes. The urine showed no abnormalities, and stool analysis was negative for blood. Roentgenograms of the chest revealed a sharply defined mass at the lateral part of the left apex, extending down to the second interspace, possibly a hemangioma. The remaining portion of the lungs, mediastinum, and diaphragms were normal. A scout film of the abdomen showed a flat density on the right which displaced the colon to the left. It had the appearance of a soft tissue mass. A presumptive diagnosis of appendical abscess was made and conservative treatment was deemed advisable. A vigorous attempt was made to improve the patient's general physical condition, and in the following twenty-four hours a total of 1,450 c.c. of citrated whole blood with additional intravenous fluids were given. Approximately forty-eight hours after admission, the child began to experience nausea, and had some projectile vomiting. There was also distention of the abdomen. The mass was now more sharply defined, more tender, and was movable. Another scout film of the abdomen demonstrated marked distention of the ascending colon, and a few loops of the small intestine. Re-examination of stools then disclosed blood, and a diagnosis of intussusception was made. Operation was carried out shortly thereafter, under pontocaine glucose spinal anesthesia. An ileo-ileal intussusception was found approximately four inches from the ileocecal valve. It was evident gangrene was present. Resection of the invaginated bowel, with end-to-end anastomosis, was carried out. Multiple hemangiomas varying in size from a pinhead to 1½ cm. were present in the jejunum and ileum, proximal to the site of anastomosis. The postoperative course was uneventful, except for a minor wound infection which rapidly

healed after the evacuation of a small amount of seropurulent material on the seventh postoperative day. The patient was discharged from the hospital on the fifteenth postoperative day, on a high protein diet which was supplemented by iron.

Pathologic Report.—Specimen consisted of a portion of ileum with intussusception. The invaginated portion of the bowel was gangrenous, and on the surface at the fulcrum of the intussuscepted bowel was a lesion which appeared grossly like a hemangioma, measuring 2 cm. in diameter. Several lymph nodes were present in the mesentery. Microscopic sections through the tumor showed large vascular spaces lined by endothelium, which were filled with old blood. The architecture of the bowel was completely disrupted, and was infiltrated with red blood cells. Marked inflammatory reaction was present. The lymph nodes showed areas of hemorrhage.

Diagnosis.—Cavernous hemangioma of the ileum; intussusception of ileum with gangrene.

SUMMARY

A patient is reported who had multiple hemangiomas of the jejunum and ileum. Acute intussusception, ileo-ileal in character, developed in this patient, resulting in gangrene of the involved bowel. This was resected without incident, and examination of the surgical specimen revealed a hemangioma at the fulcrum of the invaginated intestine. Whether this is coincidental or whether the tumor acted as the causative agent is entirely problematical.

REFERENCES

1. Lazarus, J. A., and Marks, M. S.: Benign Intestinal Tumors of Vascular Origin, SURGERY **22**: 766-779, 1947.
2. Oberhelman, H. A., and Condon, J. B.: Acute Intussusception in Infants and Children, S. Clin. North America **27**: 3-22, 1947.
3. Raiford, T. S.: Tumors of Small Intestine, Arch. Surg. **25**: 122-177, 1932.
4. Weber, H. M., and Kirklin, B. R.: Roentgenologic Manifestations of the Tumors of the Small Intestine, Am. J. Roentgenol. **47**: 243-253, 1942.

NEUROFIBROMA OF THE STOMACH

A Case Report

JOHN T. ELLIS, M.D., SAMUEL W. WINDHAM, M.D., AND
SYDNEY G. LATIOLAIS, M.D., DOTHAN, ALA.

(From Frasier-Ellis Hospital)

NEUROFIBROMA of the stomach, though a rare disease, is frequent enough to warrant consideration in a patient with bizarre and/or peculiar gastrointestinal complaints, massive gastrointestinal hemorrhage, and/or idiopathic or hypochromic anemias. Until diagnostic methods such as x-ray and gastroscopy were introduced and perfected, these tumors were pathologic curiosities for they were usually found by the pathologist at the autopsy table. More accurate and complete gastrointestinal studies as now practiced result in a higher percentage of accurate ante-mortem diagnosis.

The incidence of benign tumors of the stomach varies in series of gastric pathology reported because some series are comprised entirely of findings at the post-mortem table while others are the result of ante-mortem diagnosis and clinical material. The publication date of the series reported also makes for variation because recent series tend to show a larger percentage of this type of pathology. Lockwood[11] reported an incidence of 4.3 per cent in 278 cases of gastric neoplasms operated upon, whereas Rigler and Ericksen,[16] using autopsy material as a basis of incidence, found 11 per cent of gastric pathology to be benign tumors. Rennets[15] also using pathologic material found an incidence of 17 per cent. Paul and Chapman,[14] in 1,500 consecutive gastroscopic examinations, found only one neurofibroma. Minnes,[12] in reviewing 931 benign gastric tumors reported in the literature, found neurofibroma to occur in 10.9 per cent of cases, but in his personal series of 50 cases there was only one such tumor. Leiomyoma, polyp, neurofibroma, and papilloma occurred in that order of frequency. Judd and Hoerner[8] likewise had only 1 neurofibroma in 50 cases of benign gastric tumors. Benign gastric tumors are located in the same sites as those occupied by malignant tumors. In Judd's series, 66 per cent were in the antrum, 24 per cent in the midgastric region, and 10 per cent in the cardia. This series is representative of the reported cases.

Because of the frequency of location in the prepyloric area, these tumors frequently produce pyloric obstruction. More than 50 per cent of the patients have moderately severe to severe dyspepsia, and in approximately 25 per cent hematemesis is the presenting complaint. Bleeding is the result of ulceration over the tumor and because of chronic blood loss severe secondary anemia is a frequent finding even though there has been no frank hemorrhage. It is well known that idiopathic secondary anemia is frequently a manifestation of gastric pathology, and benign tumors including neurofibromas are occasionally the gastric pathology found. Physical findings vary from none at all to that of a large epigastric mass. There is usually slight to moderate epigastric tenderness.

Received for publication, Sept. 21, 1948.

These lesions are diagnosed by the examiner's suspecting their presence and performing a thorough and complete gastrointestinal study on the patient in whom the disease is suspected. The disease has been reported in patients ranging in age from 8 to 69 years.[2] In the laboratory the most frequent findings are a secondary anemia and/or occult blood in the stools, and positive x-ray evidence of tumor.

A positive diagnosis of neurofibroma of the stomach can be made only from microscopic study of tissue removed; however, there are definite and characteristic radiologic findings[6, 9, 13] in cases of benign tumors of the stomach. Neurofibromas fall into this classification. These findings are a filling defect produced by the intramural tumor with rugal patterns overlying this defect. These patterns are present because, for the most part, the tumor extends outward and simply displaces the mucosa over it without invading this structure. Mucosal patterns from the opposite gastric wall may produce this roentgen finding. Careful interpretation is therefore essential. In a large percentage of cases there is a central niche which has smooth and sharp contours and is usually round or oval. When the niche has a narrow mouth and branching in the deeper portion of the ulcer, it is diagnostic of benign tumor with ulceration. Except in broadly sessile tumors which exclude barium from their base producing a marginal defect, the gastric contours are well preserved. There is an absence of spasm as is found in gastric ulcer and carcinoma, and peristalsis passes over the filling defects. Ulcers atop benign tumors are as a rule not deep and the finding of the tumor is the more important of the two. This last generally accepted statement was not found to be true in the case to be reported.

To find a larger percentage of these benign tumors which may be small or large, the technique of the radiologic examination must be meticulous. A stomach filled with barium is a poor specimen in which to find these lesions. It should be the aim of the radiologist when examining a patient suspected to have a benign gastric neoplasm to simply line the stomach with barium, and add the radiopaque material as the examination progresses; in this way fewer of these lesions will be overlooked.

The pathology of neurofibromas of the stomach is essentially the same as neurofibromas located elsewhere. Mallory[3] stated that there is always some confusion as to whether these tumors should be called leiomyomas or perineural fibromas and that many of them when simply studied routinely are called myomas, whereas were they studied carefully, the true nature of the tumor would be brought out. There is a tendency for the commonly thought about neurofibroma to be multiple. Askel, in discussing gastric neurofibroma, emphasized the association of skin lesions with gastric lesions and Mallory[4] discussed one patient who had such a tumor removed, only to return at a later date with a tumor of the dorsal nerve root in the spinal canal. Our patient apparently had only the gastric tumor for he had none in the skin and no complaints which would cause one to suspect that he had one elsewhere. All agree that they are located in the wall of the stomach and that they displace the gastric mucosa ahead of them. There is some difference in opinion about the

exact layer origin. Askel stated that they arise from the gastric plexuses of nerves between the muscle layers. The tumor in our case arose immediately beneath the submucosa and displaced the overlying layers toward the gastric lumen and the muscle layers toward the serosal layer. Askanazy stated that the nerve elements within the tumor are of sympathetic origin. This cannot be confirmed either in library research or in personal communication from the leading pathologist. It is agreed by most students of this disease that they do not arise from the axis cylinder but there is again disagreement as to whether they arise from the supporting connective tissue of the nerves or from the sheath of Schwann.[1]

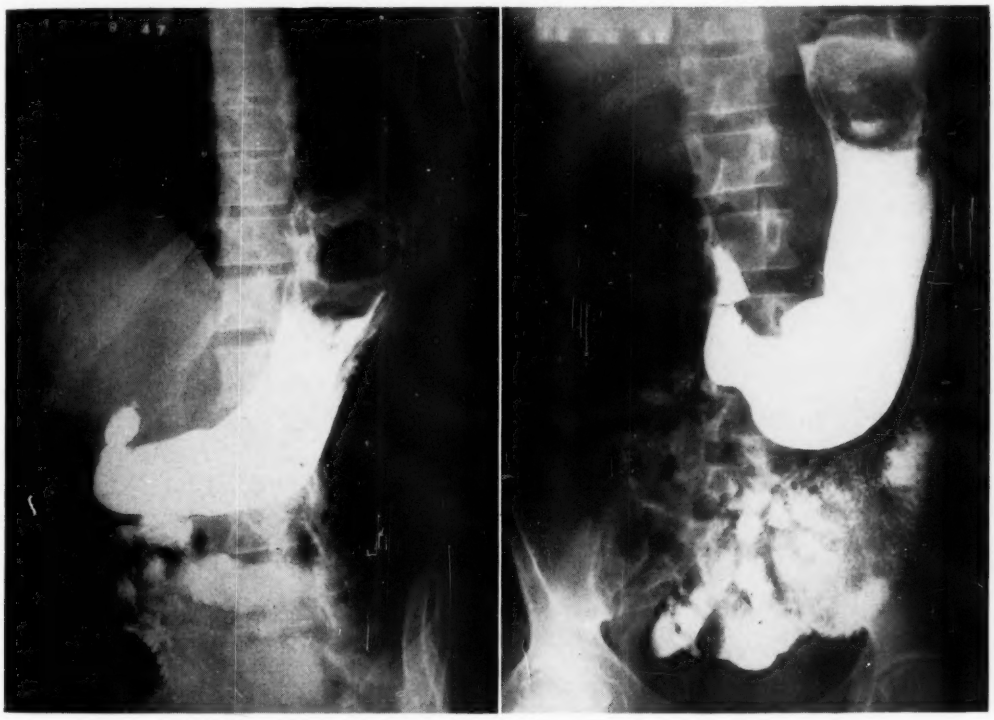
We believe that there is one characteristic of these tumors which has been neglected and that characteristic is its vascularity. In a careful study of the pathology of the tumor in the case being reported, vascular sinuses were prominent. These sinuses were located immediately beneath and communicated with the areas of ulceration. In collected series of gastric neurofibromas overlying ulceration is a most frequent finding ranging up to 32 per cent.[8] In discussing benign tumors, Hunt[7] mentioned the overlying ulceration and considered the two conditions as separate entities. Mallory[5] thought that many of the overlying ulcers are secondary to underlying vascular necrosis causing a secondary change in the overlying gastric mucosa. In the study of one case no one should become dogmatic, but in our case we feel certain that that was the etiology of the multiple gastric ulcers overlying the tumor mass. There is another pathologic characteristic which is frequently found and that is work hypertrophy of the gastric musculature.[5] This is brought about by repeated bouts of pyloric obstruction produced either by the location of the tumor or by its herniation into and/or through the pyloric ring. Mallory presented one patient whose stomach, on gross examination, appeared to have the characteristics of linitis plastica as a result of muscle hypertrophy.

Neurofibromas, though they are benign tumors, can and do undergo malignant change forming neurogenous sarcoma, and it is for this reason that we advocate surgical excision of the tumors when first found. As has been stated, unless a section of the tumor is available for miscroscopic study, benign tumors cannot be further differentiated. Lahey and Colcock[10] reported sarcomatous elements in five of seven leiomyomatous lesions of the stomach. Paul and Chapman[14] stated that 10 per cent of neurofibromas undergo malignant change, and Walters[17] advocated resection because of this tendency in the tumors. The two most frequent complications produced by the tumors, namely, hemorrhage and obstruction, ultimately will make surgery necessary. We, therefore, advocate surgical excision of these tumors to prevent these too frequent complications. If there is no doubt as to the character of the tumor, we belive that sleeve resection of the stomach is the operation of choice. If there is any doubt, gastric resection, as in any other gastric malignancy, should be performed.

CASE REPORT

L. M., a 39-year-old colored man, a shoe shop operator, entered the hospital on Dec. 10, 1947, complaining of weakness following massive vomiting of blood. Twelve days prior to admission he suddenly and without previous warning vomited a large amount of dark and

bright blood. This was associated with a dull substernal pain. He was seen by a local medical doctor who hospitalized him and put him on a modified Sippy diet. The substernal pain persisted and he had tarry stools daily. Approximately seven hours before admission he suddenly felt faint and began vomiting dark blood. He did this several times during the period from onset to hospital admission. Past history was significant in that he drank moderate amounts of alcohol and that two years before admission he began having epigastric distress which came on when the stomach was empty and was relieved by food intake. On physical examination he was found to be a well-developed and well-nourished middle-aged colored man with temperature of 100° F.; a pulse rate of 120 per minute, regular in rhythm and of fair quality; breathing rapidly; perspiring profusely; and with a blood pressure of 90/60. General examination was essentially negative, but on examining the abdomen, a poorly outlined, slightly tender mass, located in the right epigastrium, was made out. Neither liver nor spleen was palpable. Laboratory examination showed a red blood cell count of 1,200,000, a white blood cell count of 21,600, a hemoglobin which would not register on a Haden-Hausser hemoglobinometer, and a differential with a marked shift to the left in the Schilling hemogram. The urine was acid in reaction, contained no albumin nor sugar, and the microscopic examination was entirely negative. Blood was type O and Kahn reaction was negative.



A. *B.*

Fig. 1, *A* and *B*.—X-ray films showing the radiologic findings.

Numerous blood donors were procured and he was given 1,000 c.c. of whole blood on the day of admission. This same quantity was repeated on the next three successive days. On Dec. 13, 1947, the red blood cell count was 2,500,000, white blood cell count 9,800, and hemoglobin was 53 per cent. He was given an additional 1,000 c.c. of whole blood on December 15. His general well-being was much improved, and from the second hospital day, he was given a protein concentrate-milk formula in quantities of 120 c.c. every two hours. All stools were tarry in character.

On December 18, x-ray examination of the upper gastrointestinal tract was performed. Ribs, diaphragms, heart, and aorta appeared normal. The esophagus showed no filling defects or strictures. There was no evidence of varicosities in the terminal portion of the esophagus. As the barium flowed into the stomach, there was a small amount of barium clinging to the mucosa in the upper medial border of the fundus. The whole of the fundus was filled with a solid mass about the size of a man's fist. Mucosal patterns could not be identified over the surface of this tumor mass, and the extent of the base could not be made out. On fluoroscopy the duodenal cap appeared to be normal. It filled out with no evidence of spasticity. Roentgenograms made in upright and Trendelenburg positions showed this round, smooth mass filling the fundus of the stomach. On the dried films of the stomach the mass just described could be easily made out and a definite niche atop the tumor mass could be seen (Fig. 1).

Fig. 2.

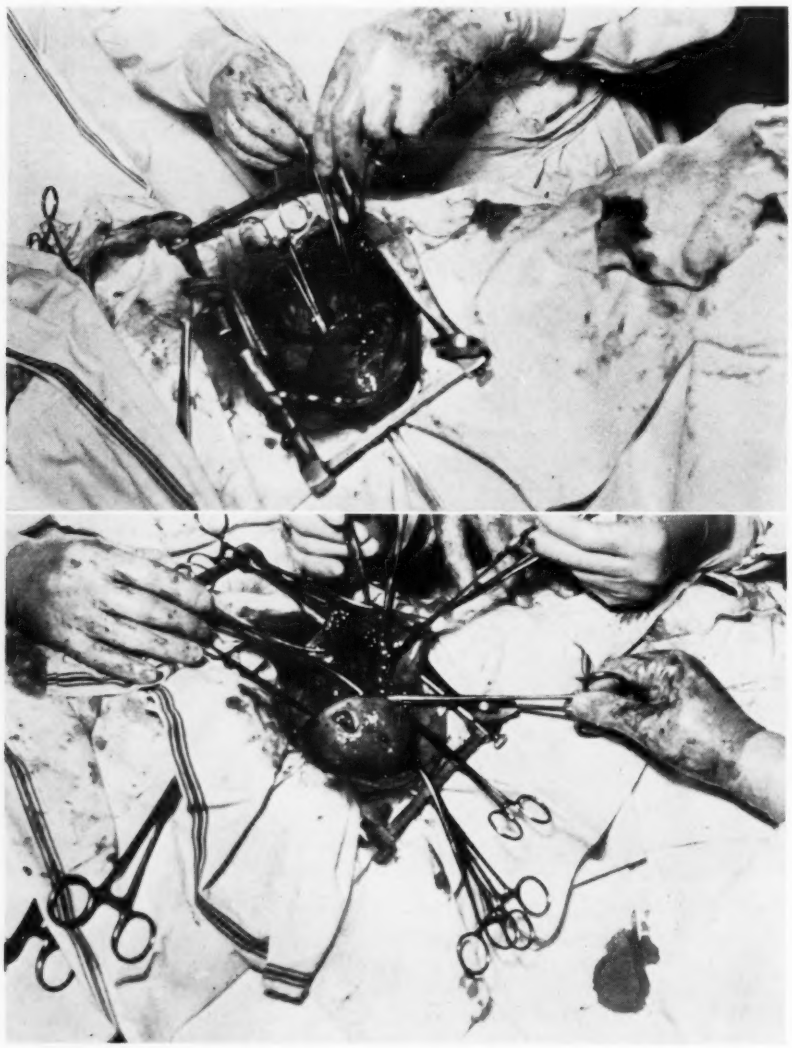


Fig. 3.

Fig. 2.—The external surface of the stomach showing the location of the tumor.

Fig. 3.—The intragastric surface of the tumor after gastrostomy showing the two ulcerations atop the tumor mass. A mass of clotted blood was located in the larger crater.

From x-ray study it was thought that the tumor was in the cardiac end of the stomach, and for that reason, it was decided that a transthoracic approach to the stomach would be the approach of choice. The gastrointestinal tract was cleaned of its contained barium, and on December 19 the patient was operated upon using a transthoracic approach. Blood was started in the vein and under intratracheal gas-oxygen-ether anesthesia supplemented by curare, the chest was entered through the ninth rib bed, the diaphragm was opened in direction of its fibers, the abdomen explored for possible metastasis, and the tumor delivered into the operative field. The tumor was well circumscribed, and no evidence of metastasis were found. It was decided that this was a benign tumor and a sleeve resection of the stomach containing the tumor was performed. Figs. 2 and 3 show the tumor in situ and Fig. 4 shows it after its removal. The excised stomach had been cut away before the tumor was sectioned and photographed. The diaphragm and chest wall were closed with a catheter drain in the pleural cavity.

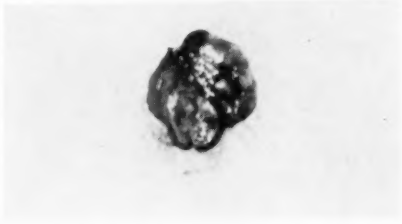


Fig. 4.—The sectioned tumor showing the character of the tumor tissue and the areas of hemorrhagic necrosis in the tumor mass.

The following is the pathologic report of the excised tumor: Gross description: The specimen consisted of an ovoid tumor mass, 8 by 5.5 by 6 cm. Covering a portion of its surface there was a membrane overlapping one end. It was a fragment of gastric mucosa, suggestively that of the pylorus. This mass of mucosa was roughly 8 by 4.5 cm. down to 1 cm. in width. Near the pole, the mucous membrane showed a deep crater deformity. The opening was 1.5 cm. in diameter and varied from 3 to 9 mm. in width; the depth of the opening was 1.5 cm. A second shallow opening was also present, located at a distance of 2 cm. from the larger one. The latter was 7 by 4 by 4 mm. deep. When sectioned, the tumor was seen to be a lobulated gray-white, rubbery, and elastic structure with areas of honeycombed deformities showing marginal reddish discoloration. The tumor appeared to be sharply outlined by a capsule. Microscopic description: Several sections of the mass show the tumor and the ulcer areas mentioned in the gross. The ulcers occurred in gastric mucosa which was completely destroyed in the ulcer area. The mucosa was of the type seen in the pylorus and showed some round-cell infiltration. There was a slight overhanging of the mucosa at the margin of the ulcers. The ulcer floor was covered with an exudate of neutrophiles in which there was some extravasation of red cells and a necrotic material covered the surface. Immediately beneath the ulcer, and apparently communicating with it, were dilated venous spaces. In surrounding tissue there was much edema. The tumor mass was situated in the submucosa and displaced the surface part of submucosa upward. The tumor nodule was sharply outlined against the embedding looser connective tissue. The tumor consisted of spindle cells that were arranged in bundles that interdigitated in various planes and were separated by vascular columns in which there was considerable collagenous connective tissue. From area to area, the cell density—or compactness of tumor—was variable. Some areas were quite cellular and the cells were thickened. In other areas the cells were separated by edema spaces. In searching many portions of the tumor, an occasional mitotic figure was seen. The tumor cells seemed to produce a small fibrillar, intercellular material. In a very occasional area there were nuclear palisades or Verokay bodies. Scattered vessels through the tumor contained clumps of neutrophiles, and in several areas there were perivascular lymphocytic infiltrations. Phosphotungstic acid stains of the tumor showed narrow

wavy and contracted fibrils produced by the tumor cells. Comment: There was some mitotic activity within the tumor tissue, but the tumor was sharply outlined and appeared to be completely removed. Figs. 5 and 6 are photomicrographs of representative sections of the tumor.

The postoperative course was uneventful. The patient was out of bed on the first postoperative day, the catheter was removed from the left pleural cavity on the third postoperative day, and the chest was aspirated on the ninth postoperative day, 600 c.c. of straw-colored

Fig. 5.

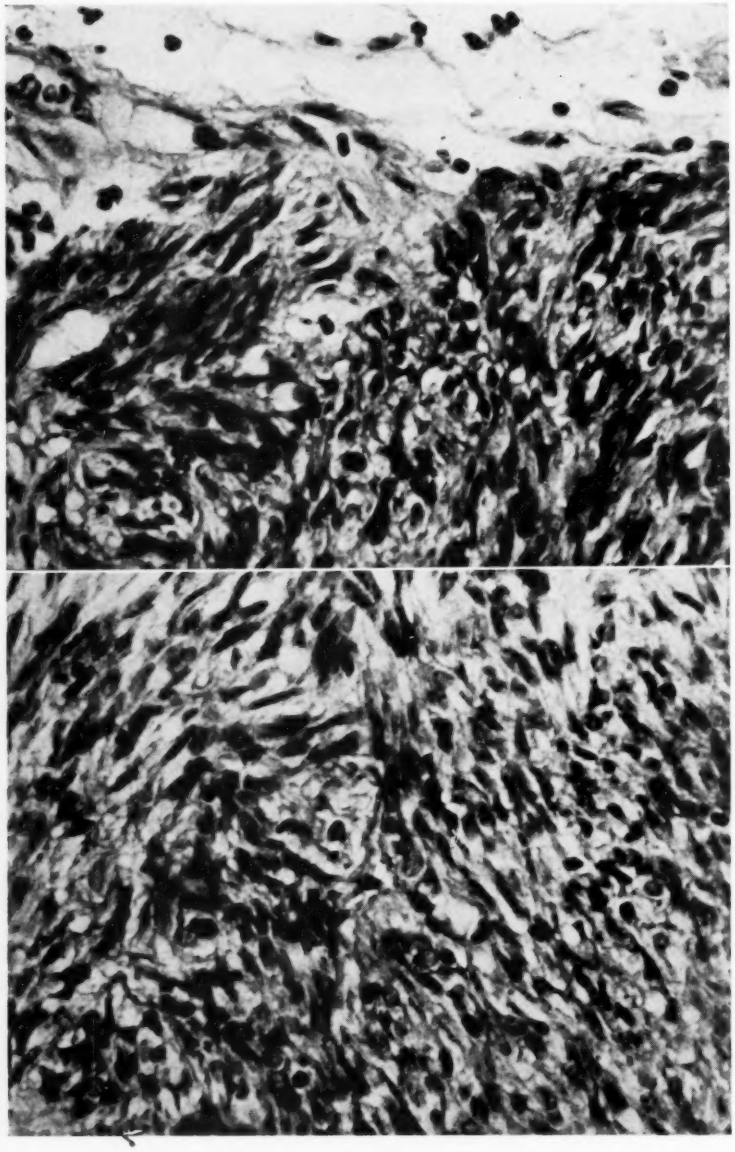


Fig. 6.

Fig. 5.—Low-power field showing the character of the tumor cells and the margin of normal connective tissue about the tumor (hematoxylin and eosin).

Fig. 6.—High-power field showing more detail of the cellular components of the tumor (hematoxylin and eosin).

fluid being removed. Following this, he was put on chest exercise, and was discharged on the eighteenth postoperative day with good and equal bilateral chest expansion and without abdominal complaints.

He has been followed through his local medical doctor and is still without complaints. He is, from the pathologic report and from symptoms, considered cured.

SUMMARY

A case of neurofibroma of the stomach has been presented along with a partial review of the literature. Its pathologic features have been discussed and especial attention called to its vascularity, pointing out that hemorrhagic necrosis in the tumor is the most probable cause of the ulcerations found in such a large percentage of these cases. When the type pathology can be definitely determined, sleeve resection of the tumor-containing stomach is the operation of choice, but when there is doubt, adequate gastric resection must be performed. The transthoracic approach to the stomach was used in the case presented, and it is considered that the patient is cured.

REFERENCES

1. Bailey, P., and Herrman, J. D.: The Role of the Cells of Schwann in the Formation of Tumors of the Peripheral Nerves, Am. J. Path. **14**: 1, 1938.
2. Balfour, D. C., and Henderson, E. J.: Benign Tumors of the Stomach, Ann. Surg. **85**: 354-359, 1927.
3. Cabot case 32161: Neurinoma of Stomach, New England J. Med. **234**: 535-537, 1946.
4. Cabot case 23361: Leiomyoma of the Stomach, N. England J. Med. **217**: 447-450, 1937.
5. Cabot case 26292: Leiomyoma of the Stomach. Case Records of the Massachusetts General Hospital, New England J. Med. **223**: 108-111, 1940.
6. Carter, R. A., and Laing, D. R.: Non-carcinomatous Tumors of the Stomach, Radiology **28**: 301-314, 1937.
7. Hunt, V. C.: Benign Tumors of the Stomach, SURGERY **1**: 711-721, 1937.
8. Judd, E. S., and Hoerner, M. T.: Benign Tumors of the Stomach, Am. J. Surg. **31**: 427-430, 1936.
9. Kirklin, B. R.: Roentgenologic Distinction of Benign From Malignant Ulcerating Lesions of the Stomach, J. Michigan M. Soc. **36**: 453-457, 1937.
10. Lahey, F. H., and Colcock, B. P.: Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach, Ann. Surg. **112**: 671, 1940.
11. Lockwood, B. C.: Benign Tumors of the Stomach, J. A. M. A. **98**: 969-973, 1932.
12. Minnes, J. F., and Geschickter, C. F.: Benign Tumors of the Stomach, Am. J. Cancer **28**: 136-149, 1936.
13. Moore, A. B.: Benign Tumors of the Stomach: From a Roentgenologic Viewpoint, J. A. M. A. **84**: 368-370, 1927.
14. Paul, W. D., and Chapman, D. W.: Neurofibroma; a Gastroscopic Report, Am. J. Digest. Dis. **12**: 258-260, 1945.
15. Rennets, J.: The Frequency and Pathological Aspects of Gastric Leiomyoma, Proc. Staff Meet. Mayo Clin. **5**: 363-372, 1930.
16. Rigler, L. G., and Ericksen, G. E.: Benign Tumors of the Stomach, Radiology **26**: 6-15, 1936.
17. Walters, W.: Benign and Malignant Tumors of the Stomach, Rocky Mountain M. J. **36**: 770-778, 1939.

COMPRESSION OF THE SPINAL CORD BY OSTEITIS DEFORMANS

Report of a Case

J. A. Colclough, M.D., New Orleans, La.

(From the Neurosurgical Service, Lakeshore Hospital)

THE first reported cases of spinal cord compression caused by osteitis deformans were those of Wyllie,[15] in 1923. In the twenty-five years which have elapsed since that time, an additional twenty-seven cases have been reported by Ardin-Delteil, Azoulay, and Lagrot;[2] Brinton;[3] Kay, Simpson, Levy, and Riddoch;[9] Vincent, Langeron, Dereux, and Lemaitre;[14] Petit-Dutaillis, Marchand, and Calderon;[11] Garcin, Varay, and Dimo;[4] Haguenau and Sicard;[7] Alessi;[1] Turner;[13] Hillman;[8] Gross;[5] and Schwarz and Reback.[12] Of the twenty-nine cases to be found in medical bibliography to this date, nineteen have had the benefit of surgical intervention with varying degrees of recovery of function. A thirtieth case of cord compression in Paget's disease is reported herewith and the twentieth case in which laminectomy has been performed, is added.* It is gratifying that in this twentieth case, neurological recovery has been complete without recurrence of the symptoms of cord involvement.

CASE REPORT

R. P.† (Case 3483), a white man, a bank teller, aged 50 years, was admitted to Lakeshore Hospital, New Orleans, La., on March 13, 1947. The chief complaint upon admission was difficulty in walking, with the minor complaints that his feet stayed asleep and that the skin burned. The patient's illness had begun about two weeks before when he began to experience difficulty in walking, which had progressively increased up to the time of admission. He stumbled a great deal and was unable to walk without assistance. He remembered that about two months before he noticed that his feet often went to sleep. This began gradually and was blamed on his shoes. Along with this, he had a marked sense of fatigue in both legs. About two weeks after the onset of the "foot trouble" the legs began to get stiff and weak. It gradually became more of an effort for him to walk. He began to grow unsteady and developed a fear that he would fall. Unsteadiness and numbness increased. The toes felt "big" and it was difficult for him to bend them one way or another. The inventory by systems revealed the fact he had no back discomfort, cranial nerve symptoms, bladder or bowel dysfunction, or change in libido or potency. The past history was that of a healthy man who had no previous illness of significance. The family history was entirely negative for neurological disease. Physical examination showed a spastic-scissors-heel type of gait. The head revealed no cranial defects or exostoses, and it was normal in size and shape. The eyes, ears, nose, and throat presented no abnormalities. There was no stiffness of the neck or limitation of motion thereof. The heart was not enlarged; there were no friction rubs or murmurs. The blood pressure was 140 systolic, 85 diastolic. The dorsalis pedis pulsations were good. The lungs were normal to inspection, percussion, and auscultation. The abdomen presented no palpable masses, tenderness, or rigidity. No organs were enlarged. There was no tenderness or deformity of the spine. The upper extremities revealed no impairment.

Received for publication, June 25, 1948.

*Since submission of this article for publication, an additional case has been reported of Paget's disease of the atlas and axis, by Norman Whalley in J. Neurol. Neurosurg. & Psychiat. 9: 84-86, 1946.

†Patient of Dr. John W. Bick, Jr., and Dr. J. O. Weilbaecher, Jr.

The cranial nerves were all normal in function. The biceps reflexes were normally present and equal. The right triceps was more active than the left. The knee jerks and ankle jerks were markedly hyperactive. The abdominal and cremasteric reflexes were absent. The Babinski sign was suggestively positive bilaterally. The lower extremities were spastic, and there was considerable muscular weakness of them. There was reduced perception of vibration over the feet, ankles, knees, and shins. Proprioception was diminished in the toes. Temperature perception was intact. There were scattered areas of hypalgesia. Perception of light touch was unimpaired. There was a band of hypalgesia occupying dorsal segments 9 and 10.

The impression was multiple sclerosis, paraplegic type, intradural neoplasm, or possible syringomyelia.

The clinical laboratory findings of significance were a fasting serum calcium of 11.1 mg., a fasting serum phosphorus of 3.6 mg., a blood phosphatase of 14 Bodansky units per 100 c.c. of serum, total cerebrospinal fluid proteins of 55 and 38 mg.[6]

A lumbar puncture revealed normal pressure and dynamics early in the patient's hospital stay. A second one made March 23, 1947, gave an opening pressure of 195 mm. of water, with a very slow rise upon jugular compression to 210, with almost no fall upon release.

The x-ray examination was reported as showing osteosclerosis involving the bodies of the sixth, seventh, and eighth thoracic vertebrae with some evidence of destruction of the body of the seventh thoracic vertebra and slight evidence of destruction of the head of the left seventh rib. The superior and inferior surfaces of the seventh thoracic vertebra are biconcave. My interpretation of this film confirmed the saucerization of the superior and inferior surfaces of the body of the seventh thoracic vertebra and I also noted compression of this vertebral body and increased density of the bodies of the sixth and eighth. There was marked osteosclerotic and osteoarthritic changes with what I took to be osteophytic fusion of these vertebrae (Figs. 1 and 2).

On March 24, 1947, lipiodal, 3 c.c., was injected cisternally and a block which was almost complete was demonstrated at the level of the seventh thoracic vertebra. A narrow space permitting slow passage of the opaque medium on the left side of the spinal canal was clearly seen with the fluoroscope and shown on a film (Fig. 3).

The preoperative diagnosis was osteoarthritis of the thoracic spine, with osteophytic fusion, causing spinal block and cord compression at the level of the seventh thoracic vertebra.

Operation.—Under general anesthesia with the patient in prone position and in very slight anteflexion, an incision was made extending from the level of the fifth to that of the ninth thoracic vertebra. The level of the block had been previously determined by myelography to be at the seventh thoracic vertebra. The soft tissues were separated from the spinous processes and laminae by means of sharp dissection and periosteal elevator and hemorrhage was controlled by means of electrocoagulation and Raney clips. The soft tissues were retracted by means of a self-retaining retractor and the spinous process and laminae of the sixth thoracic vertebra were removed by means of a rongeur. A portion of the spinous process and laminae of the fifth were also removed and the dura was exposed. Excellent pulsation of the dural sac could be felt and seen at this level. The spinous process and laminae of the eighth thoracic vertebrae and portions of those of the ninth were then removed in like manner and the dura was exposed. No pulsation could be felt or seen here. The spinous process and laminae of the seventh thoracic vertebra were then removed and during this process it was noted that the bone seemed abnormal, that it was sclerotic, and excessively porous, and at a point midway between spinous process and pedicle in the lamina on the patient's left side, a mass of soft tissue was encountered. This mass of soft tissue was approximately the size of a giant green pea, gray in color and soft in consistency. It was taken to be tumor tissue, but it did not extend down to the pedicle nor over to the spinous process. Specimens of the lamina and of the soft tissue were saved separately for examination by the pathology department. When the removal of the spinous process and of the laminae of the seventh

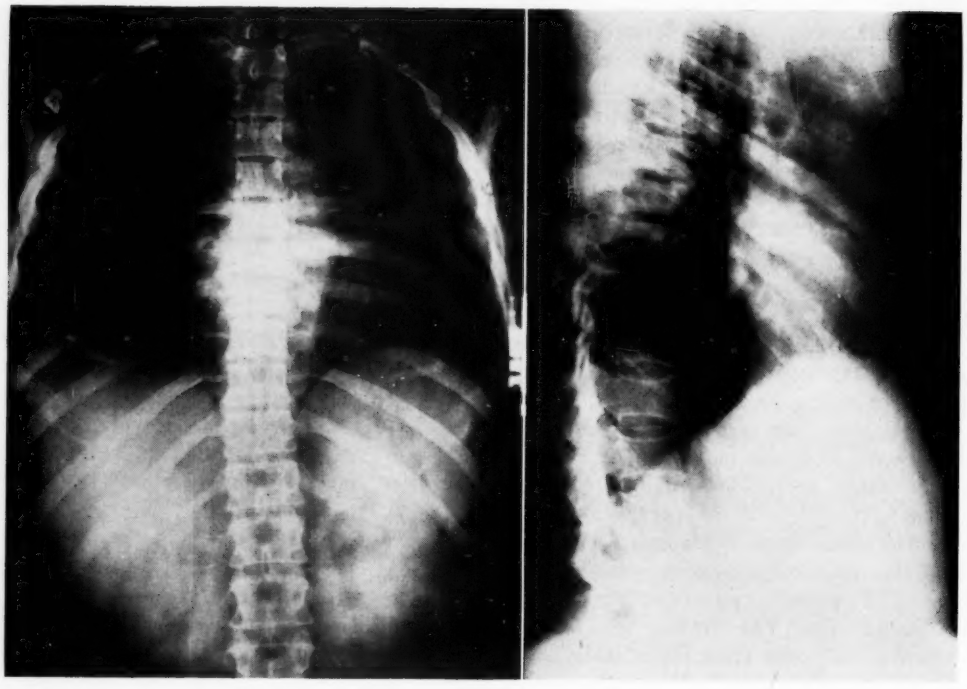


Fig. 1. Fig. 2.

Fig. 1.—Anteroposterior view of spine showing increased density of vertebral shadow in the region of the sixth, seventh, and eighth thoracic vertebrae.

Fig. 2.—Lateral view of spine showing biconcavity of the seventh thoracic vertebra.

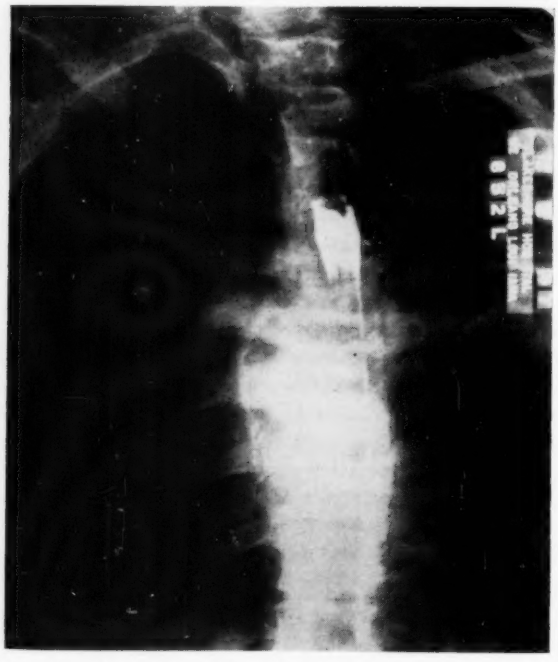


Fig. 3.—Myelogram showing almost complete block at the upper border of the seventh thoracic vertebra.

thoracic vertebra had been completed, the dural sac was pulsating throughout the extent of the exposure, that is, from the lower portion of the fifth to the upper portion of the ninth thoracic vertebra. The dura was next opened in linear fashion throughout the extent of the exposure and four sutures were placed therein to which hemostats were clamped to serve as retractors. The spinal cord appeared to be entirely normal. No intradural extramedullary mass was seen. Over the seventh thoracic vertebra, the cord seemed to be somewhat raised. It was gently retracted to one side and by means of the handle of an instrument, the floor of the spinal canal was palpated transdurally. Two transverse ridges could be felt at the upper and lower borders of the seventh thoracic vertebra, respectively. These were taken by me to be lipping of the superior and inferior borders of the vertebral body. If this condition had been single, I would have felt we were dealing with a protruding intervertebral disc, but because it was paired and because of the appearance of the vertebra by x-ray examination, I felt that the former was the case. Exploration superiorly and inferiorly within the dural sac by means of a soft rubber catheter failed to reveal any other obstruction, up as high as the sixth cervical approximately, and down as far as the first lumbar. The cord was pulsating throughout the extent of the exposure. No intradural bleeding was encountered. It was necessary to use Gelfoam and thrombin stamps extradurally, and in one place at the lower end of the wound, to use an Oxycel pack to control bleeding. The dura was closed with 0000 black silk as a continuous suture. The soft tissues, muscle, fascia, subcutaneous tissue, and skin were closed in layers using 00 black silk as interrupted sutures throughout.

Gross and Microscopic Description of Tissues.—The specimen consisted of cancellous bone chips and adherent periosteum and soft tissue. Microscopic diagnosis was bone and soft tissue from vertebral region. Sections of bone fragments showed some prominence of cement lines, which were basophilic and somewhat irregular and serrated. Bone segments were irregular, rather short, and arranged in a mosaic pattern, not forming clear-cut Haversian canals. There appeared to be some small areas of hemorrhage in the bone marrow and some fibrosis and moderate edema. Some of the sinusoidal spaces were dilated and empty. Among the bony trabeculae, there was a moderate number of osteoclasts and osteoblasts. Some of the soft tissue adjacent to the bony fragments showed a light infiltration of inflammatory cells (lymphocytes and neutrophiles). No evidence of neoplasia was found. The bone sections showed a picture which would be compatible with mild Paget's disease of bone.[10]

The patient's postoperative course was without incident. On the fourth postoperative day, he complained of a "Charley horse" in the left calf. Examination revealed no redness, tenderness, or edema, and there was no pain upon dorsiflexion of the foot or other evidence of thrombus formation. On the seventh postoperative day, the wound had healed and the sutures were removed. On the eighth day following operation a lumbar puncture revealed an initial pressure of 176 mm., with quick rise upon jugular compression to 300, and rapid fall to 176 mm. upon release.

Neurological recovery was rapid and complete. On April 5, 1947, there was about the same degree of muscular weakness and spasticity as that which was present preoperatively. The abdominal reflexes were absent. There was a zone of hyperesthesia occupying the tenth thoracic dermatome. Perception of heat, cold, pain, and touch were normal above and below this level. The knee jerks were 4 plus, the ankle jerks 2 plus. Unsustained clonus was present bilaterally and the Babinski sign was questionably positive on both sides. On April 9, 1947, no definite sensory level was found, but the tendon reflexes were hyperactive, unsustained ankle clonus was present, and proprioception was impaired in both feet. The patient was discharged from the hospital on April 10, 1947.

After the patient left the hospital the case was followed carefully. On May 7, 1947, the patient reported that he was getting stronger all the time. He seemed to have some weakness of the knees and lower back, but was able to stand for an hour at a time. He had occasional burning sensations in the legs which lasted a few seconds. Examination revealed a slightly spastic gait, with somewhat more spasticity in the right lower extremity than in the left. The knee jerks were somewhat hyperactive, the ankle jerks approximately normal. The Babinski sign was bilaterally negative. The abdominal reflexes were normally

present. There was no muscular weakness. Proprioception, perception of vibration, heat, cold, and touch were all normal. No sensory level could be found, nor were there any zones of hyperesthesia. Except for the slightly spastic gait and spasticity of the lower extremities, the neurological examination was negative.

On June 4, 1947, the patient stated that he was getting along well. He felt a little pain in the back at times and his legs tired in the evening. The spasticity had disappeared and except for a slightly hyperactive left knee jerk and an equivocal Babinski on the left, neurological examination revealed no departure from the normal.

On Nov. 14, 1947, Mr. R. P. was again seen. He had been at work since June 15, 1947, and he had no complaint except occasional slight pain in the back in the region of the operative site. I regarded his neurological recovery as complete. On Jan. 8, 1948, there was no complaint. X-ray examination at this time showed some anterior displacement of the body of the seventh thoracic vertebra, and an orthopedist was consulted (Fig. 4). He felt that a support was indicated at this time and a suitable support was prescribed and fitted. The patient has continued to work and enjoy good health.

Fig. 4.—View taken eight months after laminectomy showing slight backward displacement of the seventh thoracic vertebra.

This case seems to conform to the pattern of cases of cord compression caused by Paget's disease in most respects, except that surgery was done somewhat earlier than usual, with less cord damage, and more rapid and more complete recovery than all except a few. It differs from many in that there was no external evidence of Paget's or other spinal disease, and that there was no evidence of osteitis deformans anywhere else in the body. The roentgenographic and pathologic pictures are essentially the same as capably and completely described by other authors,[6, 10, 15] and further comment along these lines seems uncalled for. Thorough study of all cases suggestive of cord compression, careful application of the Queckenstedt by one experienced and skilled in its use

(one Queckenstedt failed to show abnormal dynamics in this case), myelographic study, and early and adequate decompression are earnestly recommended.

REFERENCES

1. Alessi, D.: Compression of Spinal Cord in Paget's Disease of Spine; Clinical Study of Case, Riforma med. **54**: 538-544, 1938.
2. Ardin-Delteil, Azoulay, R., and Lagrot: Paget's Disease of Bones With Paraplegia, Bull. et mém. Soc. méd. d. hôp. de Par. **47**: 920-924, 1923.
3. Brinton, B. M.: Paget's Disease of Spine, Causing Compression of Cord, Proc. Roy. Soc. Med. **24**: 314-315, 1930.
4. Garcin, R., Varay, A., and Dimo, H.: Acute Vertebral Legion in Paget's Disease; Transitory Quadiplegia and Brown-Sequard Syndrome; Report of Case and Study of Medullary Complications of Paget's Disease, Rev. neurol. **67**: 761-769, 1937.
5. Gross, Sidney W.: Compression of the Spinal Cord in Paget's Disease of the Vertebrae, Am. J. Surg. **55**: 575-577, 1942.
6. Gutman, Alexander B. Tyson, T. Lloyd, and Gutman, Ethel Bendict: Serum Calcium Inorganic Phosphorous and Phosphatase Activity; in Hyperparathyroidism, Paget's Disease, Multiple Myelome and Neoplastion Disease of the Bones, Arch. Int. Med. **57**: 379-412, 1936.
7. Haguenau, J., and Sicard, A.: Compression of Spinal Cord in Course of Paget's Disease: Recovery Following Operation, Rev. Neurol. **68**: 846-849, 1937.
8. Hillman, Robert W.: Compression of the Spinal Cord in Paget's Disease, Brooklyn Hosp. J. **3**: 155-162, 1941.
9. Kay, H. D., Simpson, S. Levy, and Riddoch, G.: With a Roentgenologic Section by G. E. Vilvandre, London, England: Osteitis Deformans, Arch. Int. Med. **53**: 208-248, 1934.
10. Paget, Sir James: On a Form of Chronic Inflammation of Bones (Osteitis Deformans), Tr. Med.-Chir. Soc. **60**: 37-64, 1877; reprinted in M. Classics **1**: 29-53, 1936.
11. Petit-Dutaillis, D., Marchand, J., and Calderon, Garcia: Spinal Cord Compression Due to Paget's Disease of Spine; Case Greatly Improved by Laminectomy, Rev. neurol. **66**: 71-78, 1936.
12. Schwarz, Gabriel A., and Reback, Samuel: Compression of the Spinal Cord in Osteitis Deformans (Paget's Disease) of the Vertebrae, Am. J. Roentgenol. **42**: 345-366, 1939.
13. Turner, J. A. Aldren: The Spinal Complications of Paget's Disease (Osteitis Deformans), Brain **63**: 321-349, 1940.
14. Vincent, C., Langeron, L., Dereux, J., and Lemaitre, L.: With Progressive Signs of Grave Compression of Spinal Cord; Relief by Operative Decompression, Rev. neurol. **65**: 794-799, 1936.
15. Wyllie, W. G.: The Occurrence in Osteitis Deformans of Lesions of the Central Nervous System With a Report of Four Cases, Brain **46**: 337-351, 1923.

Surgical Technique

TECHNICAL SUGGESTIONS IN THE PERFORMANCE OF TOTAL GASTRECTOMY

(1) The Posterior Esophagojejunal Buttress; (2) Use of Air-Vent Suction Drain; (3) Accompanying Coincidental Superior Mesenteric Ganglionectomy to Improve Reservoir Capacity

Owen H. Wangensteen, M.D., Minneapolis, Minn.

(From the Department of Surgery, University of Minnesota Medical School)

THE experience of surgeons with total gastrectomy, until recently, has not been a satisfying one, owing to the circumstance that operative mortality has been so high. Few clinics, even those professing a special interest in surgery of the alimentary canal over the period of the last two decades, could boast of an operative mortality of less than 30 per cent. Yet as attested in many recent reports, there has recently been a change for the better. Such too has been the experience of this clinic.

One of the fascinating things about surgery is how the fusion of a new idea or design, however simple, with old practices may change the entire complexion of a problem. One need not belabor this point. Save for periodic innovations of tradition-breaking character, which give a tremendous surge forward to all of Medicine, the story of progress in surgery is essentially that of small increments of gain in knowledge added to the common store. And occasionally a small item, inconsequential in itself, blended usefully into an operative procedure signifies the difference between frequent failure and fairly uniform success.

THE POSTERIOR ESOPHAGOJEJUNAL BUTTRESS

The addition of the simple expedient of beginning the suture in the esophagojejunal anastomosis, accompanying total gastrectomy, at the mesenteric edge instead of at the antimesenteric border has, in the experience of this clinic, made an important difference in the operative mortality of the operation. The technique of the procedure is illustrated in the accompanying diagrams. The anastomosis itself is essentially a one-row closure. The purpose of approximating the mesenteric border of the jejunum to the esophageal wall, at some distance proximal to the intended site of the esophagojejunal stoma, is to provide a buttress up against which the posterior wall of the esophagus may become firmly adherent. Then when the anterior peritoneal flap is sutured down upon the jejunum as advised by Lahey (1938), the esophagojejunal anastomosis is actually extraperitonealized or completely enclosed in an ensheathing cylinder of surrounding tissues which afford a reliable support to the suture line.

The work reported herein was supported by the Malignant Disease Research Fund of the University of Minnesota and by a grant from the Graduate School.

Received for publication, Oct. 15, 1948.

The steps in the operative procedure of total gastrectomy for gastric cancer are essentially as follows (see Figs. 1 to 4):

1. Excision of the stomach together with a segment of esophagus and duodenum

2. Excision of the entire greater omentum, spleen, and gastrohepatic omentum up to the porta hepatis

3. Inversion of the blind duodenal end

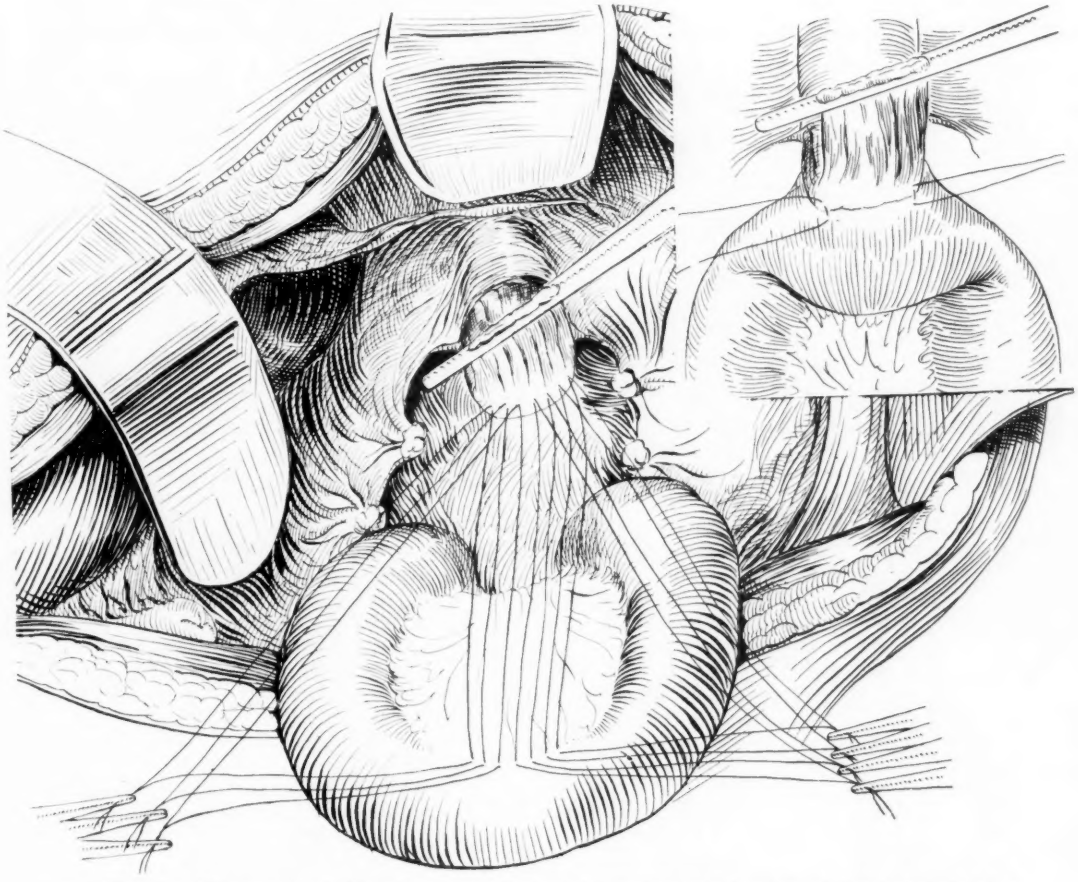


Fig. 1.—Placement of the sutures anchoring the mesenteric border of the jejunum as a buttress against the posterior esophageal wall. The employment of a 10 inch needle holder and long silk sutures (0000) 32 inches in length facilitates placement of the sutures. The insert shows the placement of a few additional sutures in a second row.

4. Retrocolic single row, open anastomosis between the esophagus and a loop of jejunum sufficiently far distant from the suspensory duodenojejunal ligament (15 to 20 cm.) to permit an enteroanastomosis between the two jejunal limbs

5. Placement of an air-vent suction drain down to the splenic bed in juxtaposition to the anastomosis.

The following are the technical maneuvers in the plan of the esophagojejunal anastomosis.

1. After removal of the stomach, the esophagus is held in a long straight clamp—an Ochsner hemostat serves the purpose well. The jejunal loop is selected for the anastomosis and laid out upon the lower margin of the incision in the anterior abdominal wall (transverse incision). Employing six to eight long silk sutures (0000) 32 inches in length and a long 10 inch needle holder, the placement of the posterior buttress between esophagus and jejunum is commenced. As is indicated in Fig. 1, the suture is begun at the mesenteric border of the jejunum. Two such rows of sutures are placed. The first row catches the posterior esophageal wall at its site of emergence through the

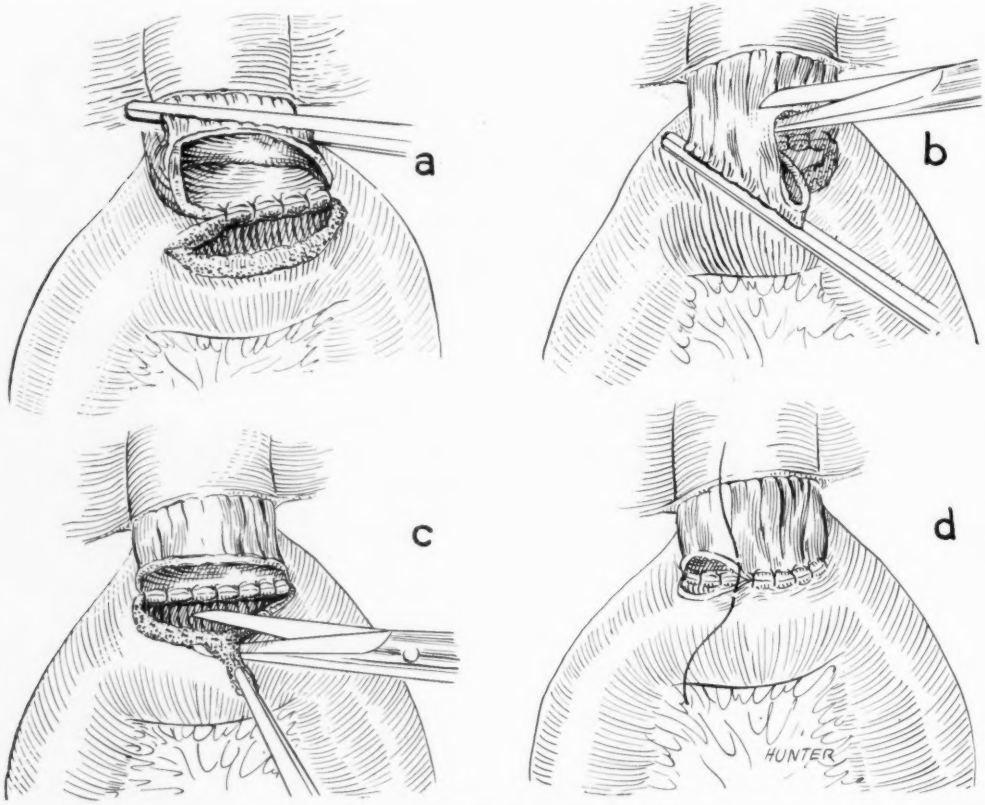


Fig. 2.—The anastomosis. (*a*) The posterior row: the clamp remains on the anterior esophgeal wall until the posterior portion of the anastomosis is completed. (*b*) Clipping away the esophageal clamp after completion of the posterior suture; (*c*) trimming away excess jejunal mucosa; (*d*) completion of the anterior anastomosis; it is to be noted that the stitch just fails to catch the mucosa on both walls, thereby affording satisfactory inversion with a single row of sutures.

diaphram; the second row is placed at an intermediate distance between the first row and the clamp on the esophagus. In tying the first row of sutures, the surgeon and his assistant each take one-half of the sutures and gently pull them up, as both surgeon and assistant, each with the aid of a "thumb-sponge" mounted on long hemostats, push the jejunum up against the esophagus.

2. After ligature of the second row of buttressing sutures, the jejunum is opened. Care must be observed not to make this opening too large. Excess or protruding mucosa is cut away. The posterior esophageal wall is then divided behind the clamp (Fig. 2, *a*) and through-and-through sutures are

placed, penetrating the entire thickness of the jejunal and esophageal walls. The clamp on the esophagus which has served as a tractor is then cut away by dividing the anterior esophageal wall. In the placement of the anterior row of sutures, the stitch just fails to engage the mucosa on both jejunal and esophageal walls, thus permitting nice inversion and approximation with a single row of sutures.

3. The anterior peritoneal flap is sutured down upon the anterior jejunal wall, care being taken to see that this flap and the posterior jejunal buttress completely surround the anastomosis.

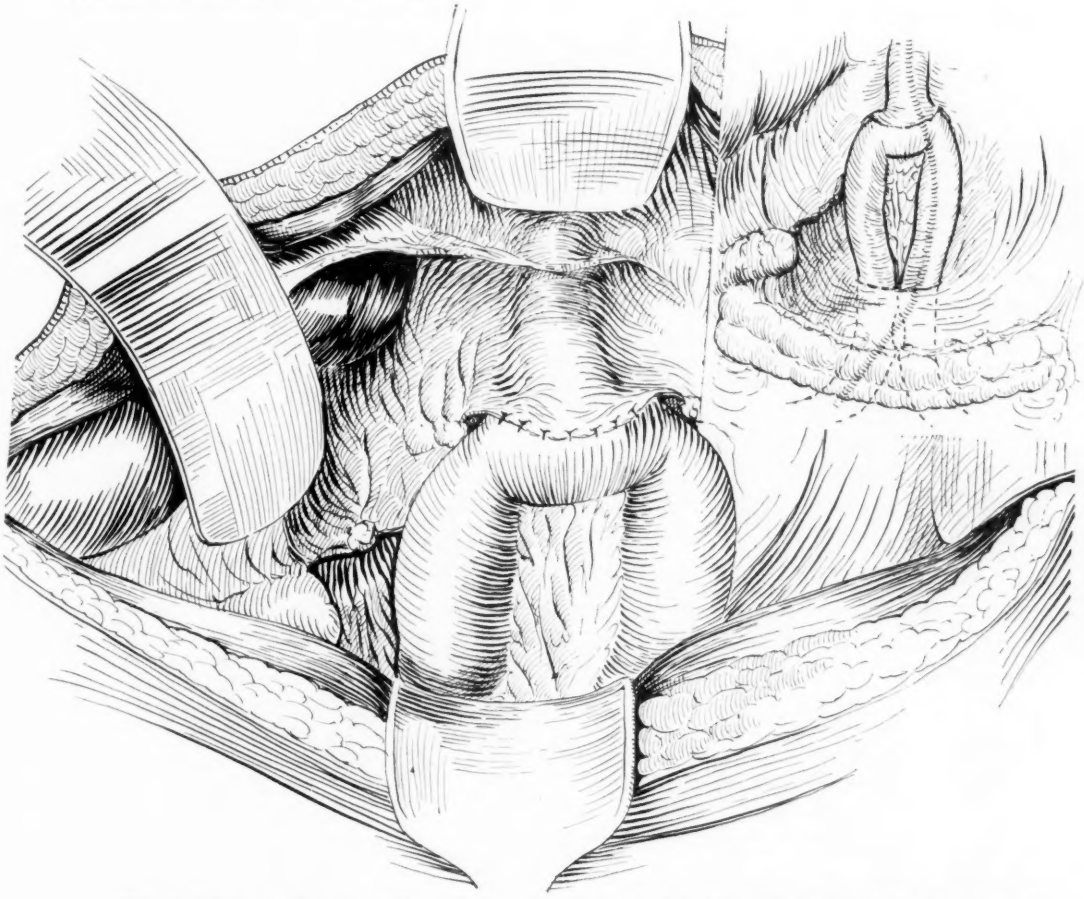


Fig. 3.—Suture of the peritoneal flap down upon the jejunum anteriorly. The insert shows the enteroanastomosis anchored beneath the slit in the transverse mesocolon. There must be no angulation at the duodenojejunal juncture. The inlying duodenal tube is threaded through the enteroanatomosis into the proximal duodenojejunal loop; it is left in place usually for approximately seventy-two hours.

Defense of the Open Anastomosis.—In this clinic over a period of approximately ten years all anastomoses in the alimentary tract, save anastomoses in which the esophagus is involved, have been made by the closed method. In an early paper on esophageal resection, Churchill and Sweet (1942) pointed out the importance of making a nice mucosal approximation in esophageal anastomosis. They stated that in order to avoid esophageal strictures, the apposition should be as careful as the restitution of the vermilion border of the lower lip

following excision of a cancer. The incidence of esophageal stricture following employment of the closed anastomosis has been such as to suggest its discontinuance. Such strictures have not been observed by me elsewhere in gastrointestinal, colic, or rectal anastomoses following resections employing the closed technique. The reason for such stricture formation following closed anastomoses in the esophagus is quite obvious to anyone who has had experience with the open anastomosis. Unlike intestinal or colic mucosa which pout into the wound, following incision of the bowel wall, esophageal mucosa not infrequently retracts following removal of the clamp, such that, in performing the open anastomosis, the surgeon must observe great care lest he fail to catch the

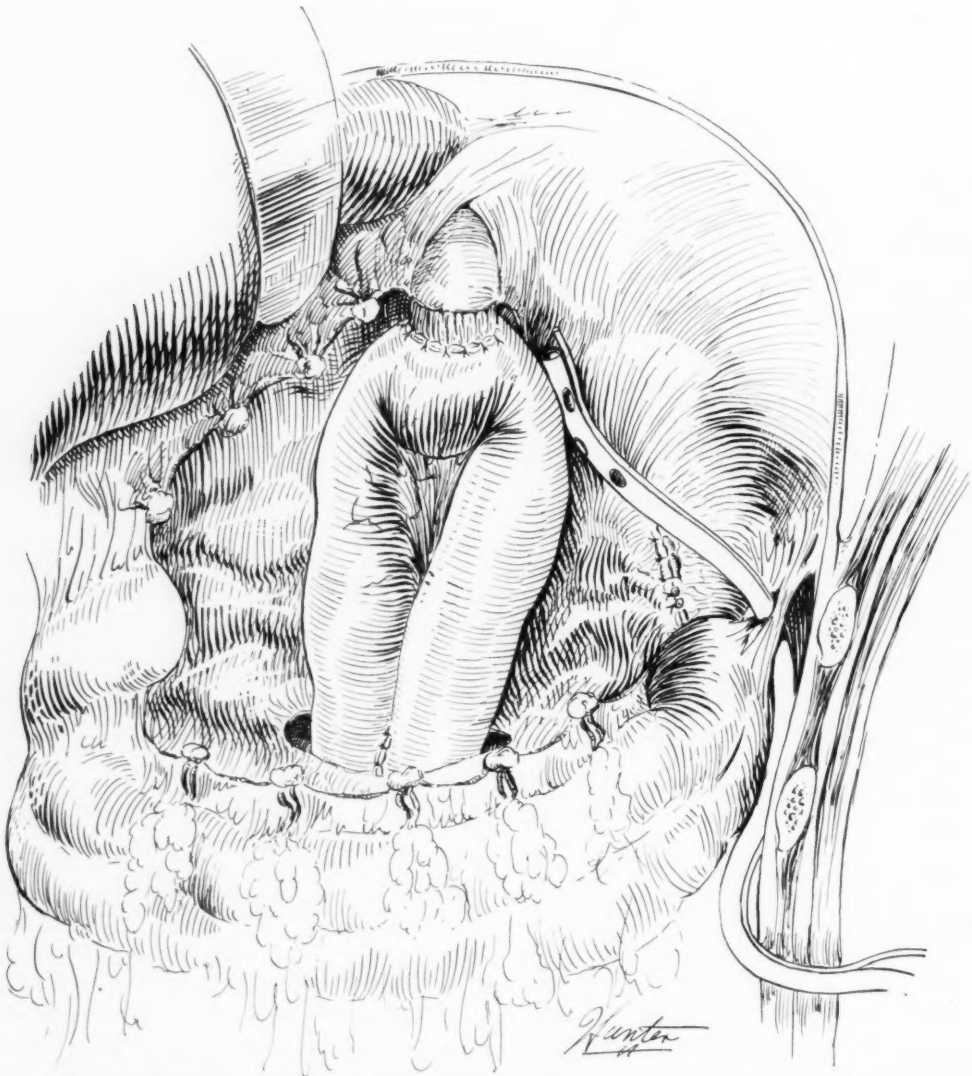


Fig. 4.—The air-vent suction drain in place. The drain is assembled at the operating table. A small No. 10 or 12 French catheter, with the end cut off, such that a single opening is present only at the tip, is fastened by a few silk ties to a 22 French rectal tube into which additional apertures have been cut. The tip of the small catheter projects 1 to 2 cm. beyond the larger one thus affording best assurance, as air is displaced by suction through the wound, that the wound will be maintained dry. Latterly, plastic tubes of the same relative sizes, which provoke less tissue reaction than rubber, are employed.

esophageal mucosa in the through-and-through posterior suture. By deliberately passing the needle deeply enough to catch the esophageal mucosa, it may prove feasible to employ the closed anastomosis and still avoid stricture formation. The tendency to stricture following the closed anastomosis in my hands, however, has been such as to suggest definitely the superiority of the open over the closed anastomosis in esophageal suture. In any case, the open anastomosis made by the technique described herein, in which mucosal apposition in the anterior portion of the anastomosis is omitted in the interest of obtaining satisfactory inversion with a single row of sutures, appears to protect against stricture formation.

It perhaps is not out of place to point out here that the technique of dilating an esophageal stricture following total gastrectomy in which an enteroanastomosis is made coincidentally between ascending and descending limbs of the jejunum is not a simple problem. Dilatation of the stricture over a swallowed silk thread is inadvisable, for the thread may wrap itself around the enteroanastomosis and become so tight in the process that the thread cuts through the bowel wall into the mesentery causing fatal hemorrhage—an occurrence which has been observed here. Development of a new technique of dilating esophageal stricture in the presence of an enteroanastomosis obviously is needed to avoid this complication.

4. An enteroanastomosis is made between the ascending and descending jejunal limbs and the slit in the transverse mesocolon is anchored by a few sutures to the adjacent bowel wall. Moreover, additional sutures are placed to obviate the possibility of herniation of coils of small intestine between the ascending and descending limbs of the jejunum as well as beneath their common mesentery.

There is one point with reference to the length of the afferent loop as well as its direction which merits special attention. It must be long enough so that there is no tension on it; moreover, great care must be observed to avoid angulation at the duodenojejunal angle. Strange as it may seem, upon withdrawing the indwelling duodenal tube lying in the proximal duodenal loop, I have observed a closed-loop obstruction develop in that loop, owing to a slight twist in the bowel in its ascent to the esophagus—an angulation at the duodenojejunal juncture which was followed by gangrene of the proximal duodenal loop. No protection was afforded by the enteroanastomosis which lay just distal to the duodenojejunal angle. In other words, in selecting the jejunal loop for the esophagojejunal anastomosis, the surgeon should take pains to avoid the slightest suggestion of angulation when he migrates the jejunal segment upward. Moreover, he probably will do well to sever the tethering membranes of the duodenojejunal ligament, thus increasing the mobility of the gut at this juncture.

USE OF THE AIR-VENT SUCTION DRAIN

In this clinic, a 95 to 98 per cent gastric excision was done for the hemorrhagic diathesis of portal hypertension in a few patients over a five-year interval with some success. A deterrent to total excision of the stomach was the greater safety of leaving 2 to 5 per cent of the stomach for the anastomosis. Since total gastrectomy has become a safer operation, it is now preferred in this clinic

over the virtual total gastric excision in dealing with the hemorrhage of "esophageal varices" in portal hypertension, a procedure which Phemister and Humphreys (1947) recently also have endorsed. Experience with total gastrectomy in the presence of portal hypertension has taught an important lesson with reference to the performance of total gastrectomy. A failure occasioned by the accumulation of fluid about the anastomosis incident to the portal hypertension may mar an otherwise satisfactory result. Abdominal surgeons are quite familiar with the circumstance that a subphrenic collection in juxtaposition to an anastomosis may threaten the security of the suture line. In this respect, a subphrenic abscess, because of the likelihood of inviting fistula formation in the presence of a near-lying anastomosis, holds out a far more serious threat than does a similar abscess in the absence of a recent anastomosis in the alimentary tract. That an innocent collection of fluid also may eventuate more readily in an abscess accompanying an intestinal anastomosis, especially of the open type, is obvious too. It was surmised that portal hypertension might invite fluid collection about the anastomosis. In consequence, an air-vent suction drain of the sump type (Babcock, 1947, or Chaffin, 1946, depicted in Fig. 4) has been placed regularly in the splenic bed (the spleen being excised) behind the esophagojejunal anastomosis in total gastrectomy. The aspiration of 70 to 300 cm. or more fluid a day has not been unusual.

My associate, Dr. Ivan Baronofsky, has made an important and unexpected observation with reference to the character of the fluid in a few such instances. In a patient with rather profuse drainage through the air-vent suction drain, a few days after total gastrectomy performed by me, the fluid exhibited a whitish, opalescent quality which suggested to Dr. Baronofsky that it might be pancreatic juice. And such it proved to be, the fluid containing as much amylase as is found in pure pancreatic juice. There had been no apparent injury to the tail of the pancreas noted by me in the operation. The same circumstance has been noted accompanying simple splenectomy. And it may well be that some of the febrile reactions noted in patients occasionally a few days following splenectomy may be owing to this occurrence. Whether this circumstance concerns injury to the blood supply of the tail of the pancreas by including the tip of the tail in the ligature of the splenic vessels, or whether it concerns severance of tiny pancreatic ducts attached to the splenic hilum, remains to be resolved. In any case, it is an observation not without consequence for the abdominal surgeon whenever he excises the spleen.

Moreover, employment of this simple device of placing an air-vent suction drain beside the esophagojejunal anastomosis in total gastrectomy has shortened the hospital stay such that dismissal from the hospital approximately seven to ten days after operation is usual.

COINCIDENTAL SUPERIOR MESENTERIC GANGLIONECTOMY

One of the frequent complaints of patients who have undergone total gastrectomy is reduced capacity for the ingestion of food. This occurrence is

by no means uniform. Several years ago, a patient was observed whose appetite following total gastrectomy was subjectively the very same as it had been before excision of the stomach and division of the vagi nerves. In the main, loss of the gastric reservoir is a handicap that bothers many patients for long intervals after total gastrectomy.

Splenectomy has been a constant accompaniment of total gastrectomy for many years in this clinic. When the spleen and the stomach have both been removed, the pancreas may readily be displaced to the right by the addition of a few snips of the scissors in the transverse mesocolon where it appears to fuse with the pancreas. This maneuver bares the superior mesenteric vessels, permitting decortication and removal of the adventitious tissue including the nervous plexus covering the root of the superior mesenteric artery. The superior mesenteric artery is cleared of nervous fibers and adventitious tissue for a distance of at least 3 cm. as is also the site at which the superior mesenteric artery takes its origin from the aorta. This postganglionic removal of sympathetic fibers from the superior mesenteric artery should remove the painful stimulus caused by distention of the small intestine, thus making it possible for the patient after total gastrectomy to eat in larger amounts. This procedure has been carried out in five of the abdominal total gastrectomies reported herein. Some of these appear to have acquired a larger reservoir capacity earlier after operation than is usual. A deterrent to routine incorporation of this maneuver as a regular part of total gastrectomy is that a postganglionic sympathectomy, such as this is, does augment the motility of the small intestine and may provoke a temporary diarrhea. Diarrhea may attend total gastrectomy unaccompanied by removal of the superior mesenteric ganglion; moreover, in my experience, removal of the superior mesenteric ganglion alone, leaving the inferior mesenteric ganglion intact, has not provoked persistent diarrhea whether accompanied by total gastrectomy or not. Excision of the superior mesenteric ganglion may prove a useful expedient to insure a good arterial inflow in those cases in which a long loop of jejunum is to be transferred into the chest to replace all or a part of the esophagus. Postganglionic section of the sympathetic outflow to the small intestine, like preganglionic section, as advised by Ray and Neill (1947) for certain types of abdominal pain, should eliminate pain accompanying intestinal distention—a circumstance which has desirable as well as undesirable features.

OPERATIVE MORTALITY

Over an interval of somewhat more than two years, since the expedient of employing the jejunal wall as a posterior buttress has been employed in this clinic (up to Aug. 1, 1948) 28 consecutive total gastrectomies have been done; of these, 24 were total gastrectomies carried out through the abdomen· in 4 instances, a combined thoracoabdominal approach was employed. The operations were done by eight surgeons. There was one hospital death in the group (abdominal total), a hospital mortality of 3.5 per cent. Of the 28 total gastrectomies, 15 were done by me; of this number, 12 were abdominal total excisions and 3 were total gastric excisions done through the combined approach. There were no hospital deaths in this small series of 15 cases—an experience

rather gratifying and contrasting sharply with previous disappointments encountered in various skirmishes with the technical problem of total gastrectomy prior to employment of the posterior jejunal buttress.

ULTIMATE OUTLOOK

In my experience, total gastrectomy is carried out often as a palliative operation. That is, it is done not infrequently for large cancers, often accompanied by obvious metastases to the local lymph nodes and broad areas of fixation of the tumor to adjacent organs or tissues. In other words, whereas surgeons are learning to cope with the problem of performing total gastrectomy with a reasonable mortality, the outlook in the conventional total gastrectomy as performed today for advanced gastric cancer is not good. If a better showing is to come about with this operation, it is mandatory that gastric cancer like other silent malignancies of the alimentary tract be recognized earlier. Gastric cancer *is* curable if removed before the lymph nodes are involved. The experience of this clinic suggests that approximately a 50 per cent five-year survival rate is to be anticipated if the gastric cancer is removed and the adjacent lymph nodes are found to be free of metastases. Longmire's (1947) suggestion of performing total gastrectomy for most gastric cancers will extend the cure rate among the survivors of operation in those patients with diffuse mucosal or submucosal spread of the cancer, a circumstance difficult or impossible to detect at the operating table or on gross inspection of the resected specimen.

SUMMARY

An adjuvant measure for insuring greater safety in the performance of total gastrectomy is described. It consists in buttressing the jejunal wall against the posterior wall of the esophagus, thus permitting complete enclosure of the esophagojejunal anastomosis in a firm ensheathing cylinder of supporting tissues when the subdiaphragmatic esophagus is sutured down upon the jejunum anteriorly.

The importance of maintaining a dry healing site about the anastomosis through employment of a temporary air-vent suction drain attached to a "flea" motor is emphasized.

The experience of this clinic suggests that total gastrectomy may be done with an operative mortality which is not much out of line with that accepted by practiced surgeons for partial gastrectomy. In twenty-eight consecutive total gastrectomies done at the University Hospitals over a two-year interval, there was one hospital death, a mortality of 3.5 per cent. Total gastrectomy is done frequently now as a palliative operation and until earlier recognition of silent gastric cancer becomes more frequent, the outlook of total gastrectomy as a curative operation for gastric cancer is rather dismal.

ADDENDUM

In large gastric cancers which involve the cardiac end of the stomach, upward spread of the cancer in the muscles of the esophageal wall for a few centimeters is not unusual. This circumstance is one of the deterrents to complete excision of the lesion by total gas-

trectomy from within the abdomen, and an occurrence which suggests the wisdom of free use of a combined abdominothoracic approach. The incision employed by my colleague, Arnold J. Kremen (SURGERY **24**: 605, 1948) was designed especially to meet this circumstance in total gastrectomy and for the primary cancer of the esophagus in its juxtacardiac position.

We speak of the esophageal hiatus. The crura of the diaphragm really convert it into a canal. By dividing the crura of the diaphragm, and particularly the right crus as described by the English surgeon, Ivor Lewis (Brit. J. Surg. **34**: 18, 1946) and more recently by J. E. Macmanus (SURGERY **24**: 9, 1948) it is not difficult to pull down and excise with the stomach from below 3 to 5 cm. of esophagus and effect an anastomosis with the jejunum without tension. And this can be done rather easily without opening the pleura. This maneuver does away with one of the limitations of abdominal total gastrectomy for gastric cancer and should come to be standard practice in the operation.

In a patient with cardiospasm who had a large dilated atonic esophagus and a pinchcock-like effect at the lower end, the division of the right crus of the diaphragm permitted pulling down of several centimeters of the esophagus thus straightening out quite satisfactorily the course of the thoracic esophagus from within the abdomen. Excision of 10 cm. of esophagus and the upper fourth of the stomach, accompanied by an esophagogastric anastomosis, was followed by shrinkage in the size of the lumen of the remaining esophagus as well as by disappearance of the difficulty in swallowing.

REFERENCES

1. Babcock, W. W.: Newer Methods of Abdominal Drainage, Arch. Surg. **54**: 365, 1947.
2. Baronofsky, I. D.: Unpublished observations, 1947.
3. Chaffin, R. C.: Vesicovaginal Fistula; Improvement in Chaffin Method of Postoperative Treatment Using Chaffin Suction Drainage, Am. J. Surg. **71**: 305, 1946.
4. Churchill, E. D., and Sweet, R. H.: Transthoracic Resection of Tumors of Esophagus and Stomach, Ann. Surg. **116**: 566, 1942.
5. Graham, R. R.: Technique for Total Gastrectomy, SURGERY **8**: 257, 1940.
6. Jones, T. E., and Kehm, R. W.: Total Gastrectomy, Report of 8 Cases, Surg., Gynec. & Obst. **80**: 534, 1945.
7. Lahey, F. L.: Complete Removal of the Stomach for Malignancy With a Report of 5 Surgically Successful Cases, Surg., Gynec. & Obst. **67**: 212, 1938.
8. Longmire, W. P., Jr.: Total Gastrectomy for Carcinoma of the Stomach, Surg., Gynec. & Obst. **84**: 21, 1947.
9. Moore, G. E., State, D., Hebbel R., and Treloar, A. E.: Carcinoma of the Stomach: The Validity of Basing Prognosis Upon Borrmann Typing or the Presence of Metastases, Surg., Gynec. & Obst. **87**: 513, 1948.
10. Phemister, D. B., and Humphreys, E. M.: Gastro-esophageal Resection and Total Gastrectomy in the Treatment of Bleeding Varicose Veins in Bartis' Syndrome, Ann. Surg. **126**: 397, 1947.
11. Ray, B. S., and Neill, C. L.: Abdominal Visceral Sensation in Man, Ann. Surg. **126**: 709, 1947.
12. Smith, F. H.: Total Gastrectomy; Report of 89 Cases, Surg., Gynec. & Obst. **84**: 402, 1947.
13. State, D., Moore, G. E., and Wangensteen, O. H.: Carcinoma of the Stomach; a Ten Year Survey (1936-1945 Inclusive) of Early and Late Results of Surgical Treatment at the University of Minnesota Hospitals, J. A. M. A. **135**: 262, 1947.
14. Wahren, H.: Total Resection of the Carcinomatous Stomach, Acta. chir. Scandinav. **95**: 193, 1947.
15. Wangensteen, O. H.: High Gastric Resection in Cancer of the Stomach With Relation of Personal Experiences, Lancet **57**: 1, 1937.
16. Wangensteen, O. H.: The Ulcer Problem: 1. Etiology With Special Reference to an Inter-relationship Between the Vascular and the Acid-peptic Digestive Factors; 2. Characterization of a Satisfactory Operation Which Will Protect Against Recurrent Ulcer, Canad. M. A. J. **53**: 309, 1945.
17. Wangensteen, O. H.: The Problem of Gastric Cancer, J. A. M. A. **134**: 1161, 1947.
18. Wangensteen, O. H., and Carlson, H. A.: Hunger Sensations in Patient After Total Gastrectomy, Proc. Soc. Exper. Biol. & Med. **28**: 545, 1931.

Editorial

The Duodenal Ulcer Problem

THE following editorial by Dr. Puderbach is provocative. It takes the position that removal of the ulcer as a part of radical gastric resection adds little, if anything, to the final result. This concept, not new in itself, deserves study. Dr. Fitts, in the second editorial, takes issue with two assumptions made by Dr. Puderbach.

Why Remove the Duodenal Ulcer?

The basic goal of all present and past surgical techniques advocated for the treatment of duodenal ulcer is to produce by various methods either neutralization, diminution, or abolition of gastric acid secretion. It is fairly well established that ulcer formation is merely a secondary effect of excessive acid secretion. Unquestionably at the present time subtotal gastric resection, whether or not combined with vagotomy, is used in most of the cases surgically treated. The crux of a successful gastrectomy appears to lie in complete excision of the gastric antrum. There is still, however, considerable confusion in the minds of many surgeons as to how the ulcer itself should be treated. An increasing volume of evidence shows that a more conservative attitude is in order toward the type of duodenal ulcer which is difficult to remove. This ulcer usually produces problems of duodenal stump closure and after its excision frequently gives rise to serious and, at times, fatal complications. Indeed, most postoperative difficulties are those arising from the duodenal stump.

Theoretically, the beneficial effects of an adequate gastrectomy are achieved by the elimination of one of the three phases of gastric secretion, namely, the gastric phase. Complete removal of the mucosa of the gastric antrum is essential to assure abolition of the hormonal gastrin mechanism residing here, since the elaboration of gastrin initiates the second or gastric phase of digestion. Retention of even a minimal portion of the antrum is known to result in persistent acidity which may invalidate the effects of surgery and lead to gastrojejunal ulceration. What is less well established is the problem as to what is essential in dealing with the ulcer as found at operation. Must every ulcer be removed? An ulcer in the first portion of the duodenum (where the majority are situated), which is easily accessible and easily dissected free, should probably be removed if for no other reason than to present the pathologist with a specimen and the surgeon with a sense of achievement. No such unanimity of opinion exists when discussing ulcers more distally situated.

Some outstanding surgeons have gone to great lengths to impress upon the profession their beliefs that complete removal of the duodenal ulcer is essential in every case, one authority advocating a second operation for this purpose even though the patient may be entirely symptom-free following a gastrectomy in which the ulcer was not, or could not, be dissected free. The danger of perforation, persistent ulcer activity, or the threat of eventual marginal ulcer is cited as the reason for the alleged necessity of a second operative procedure. Others confronted with a difficult stump closure where extensive resection was required to excise a low-lying ulcer have devised ingenious procedures such as the fashioning

of flaps to achieve duodenal closure. The use of T tubes and close direct observation of the common duct is believed by some to be necessary to prevent subsequent bile duct strictures and trauma to the structures in the portal triad when carrying out gastrectomy.

To excise the relatively distal lying ulcer requires delicate dissection and manipulation of such structures as the duodenum itself with its inadequate collateral blood supply, the very vascular and easily traumatized pancreas, and the vulnerable portal triad. This is the ulcer which gives rise to most of the complications encountered in gastrectomy. In an easily accomplished operation we do not often encounter such sequelae as duodenal necrosis, leakage, abscess, fistula, pancreatitis, common duct stricture, or obstruction. Inept or overzealous attempts to excise these ulcers account for most of the postoperative complications.

If, as postulated, subtotal gastrectomy cures the ulcer diathesis by the abolition of the gastrin mechanism of the antrum, then the excision of a duodenal ulcer should not be necessary in the performance of gastric resection except perhaps in cases of hemorrhage or threatened perforation. The patient is thereby needlessly subjected to additional surgical trauma and risk.

In cases where removal of the ulcer is difficult or not feasible, better results are obtained by leaving the ulcer alone. Many authorities view the retention of such an ulcer with equanimity and profess little alarm over alleged eventual complications. One wonders how often the ulcer is inadvertently either completely or partially incorporated into the duodenal stump upon closure. It is well known that the pathologist frequently cannot recognize ulcer pathology in a surgical specimen because the clamps applied prior to transection of the duodenum have traversed the ulcer bed or because the ulcer was unwittingly incorporated into the duodenal stump by suture inversion.

The recent surgical literature is replete with articles advocating a simpler approach to this problem by such methods as excision of antral mucosa, simple closure over the ulcer, etc.

There is no scientific basis for excising every duodenal ulcer in every gastric resection. Ulcers which are easily removed and which leave a duodenal stump of adequate length for secure closure may be excised at the option of the surgeon, but it is well to remember that the principle underlying gastrectomy is *not* excision of the duodenal ulcer but removal of its cause by excision of the gastric antrum.

—*Walter J. Puderbach, M.D.*
Brooklyn, N. Y.

REFERENCES

1. Allen, A. W., and Welsh, C. E.: Subtotal Gastrectomy for Duodenal Ulcer, Ann. Surg. **124**: 688, 1946.
2. Cattell, R. B.: The Use of the Long T Tube in Surgery of the Biliary Tract, S. Clin. North America, 659, 1948.
3. Judd, E. S.: Present Status of Surgical Treatment of Duodenal Ulcer, J. Kansas M. Soc. **49**: 1, 1948.
4. Gardner, C. E., and Hart, D.: Surgical Treatment of Peptic Ulcer, Ann. Surg. **127**: 1056, 1948.
5. Gaviser, D.: Evaluation of 416 Cases Operated Upon for Peptic Ulcer, SURGERY **24**: 871, 1948.
6. Nissen, R.: Duodenal and Jejunal Peptic Ulcer, Technic of Resection, New York, 1945, Grune & Stratton, Inc.
7. Priestley, J. T.: Physiologic and Surgical Considerations in the Treatment of Duodenal Ulcers, California Med. **67**: 1, 1947.

Comments on Dr. Puderbach's Editorial

Dr. Puderbach's editorial is timely. His thesis—that the duodenal ulcer that is difficult to excise should not be disturbed during gastrectomy—has not been widely advocated. The editorial correctly points out that most complications of partial gastrectomy arise from difficulties in removing the ulcer or from inadequate duodenal closure following removal of the ulcer.

Two of Dr. Puderbach's assumptions warrant further discussion. The first is that the duodenal ulcer remaining after gastric resection is innocuous. Is there, as yet, adequate clinical or experimental data to show that the retained ulcer does *not* predispose to the production of free hydrochloric acid with the formation of marginal ulcer and to the local complications of perforation and hemorrhage? In studies of patients who developed marginal ulceration following gastrectomy, a high incidence of retained ulcer has been reported by experienced clinicians; they have expressed the opinion that the presence of the duodenal lesion predisposed to the formation of marginal ulcer. But did the patients who developed marginal ulcer have enough stomach excised? May not the marginal ulcer have been due to an inadequate gastric resection rather than due to the retained ulcer? These questions should be further studied by competent clinical investigators.

Second, Dr. Puderbach states that removal of the gastric antrum cures the ulcer diathesis. The importance of the gastric antrum in the hormonal control of acid formation is generally accepted. A gastric resection that leaves antral mucosa is an inadequate operation. It has been shown, however, that resections limited to the excision of the antrum are complicated by a high incidence of marginal ulceration. Lannin found that excision of the antrum did not protect dogs from ulceration induced by injections of histamine in beeswax. In contrast a resection that removed three-fourths of the stomach gave protection. Wangensteen and Lannin noted a 33 per cent incidence of marginal ulcer in a small series of patients who had resections limited to the antrum. Oliver found that in the "Mann-Williamson dog," with the duodenal and pancreatic secretions drained into the terminal ileum, jejunal ulceration was not completely prevented by even a three-quarters resection. Only a total gastrectomy gave complete freedom from ulcer. It appears that removal of more than the antrum is required to control the production of acid and the secondary formation of ulcer.

It is probable that a gastric resection adequate to insure cure of duodenal ulcer must remove at least three-fourths of the stomach including all of the gastric antrum. If this is effected, removal of the ulcer may add little, if anything, to the final result. From the data now available it would appear dangerous to combine retained ulcer with excision of no more than the gastric antrum.

—*William T. Fitts, Jr., M.D.*
Philadelphia, Pa.

REFERENCES

1. Lahey, F. H.: Inflammatory Lesions of the Stomach and Duodenum, J. A. M. A. **127**: 1030-1036, 1945.
2. Lannin, B. G.: Experimental Evaluation of a Satisfactory Operation for Ulcer, SURGERY **17**: 712-741, 1945.
3. Wangensteen, O. H., and Lannin, B. G.: Criteria of an Acceptable Operation for Ulcer: Importance of Acid Factor, Arch. Surg. **44**: 489-500, 1942.
4. Oliver, J. V.: Effect of Gastrectomy and Diversion of Duodenal Secretions Into Distal Ileum Upon Development of Jejunal Ulcers, Bull. Am. Coll. Surgeons **34**: 34, 1949.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE DESIGN AND MANAGEMENT OF LONG INTESTINAL TUBES

JOHN J. WILD, M.D., MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota Medical School)

FOLLOWING the treatment of the obstructed bowel by means of an in-lying gastroduodenal tube with continuous applied suction by Wangensteen,[1] the introduction to surgery of the long intestinal tube by Abbott and Johnston[2] was hailed as an important advance in the management of intestinal distention. There is now in most quarters little doubt as to the value of decompressing the distended bowel, but the means of bringing about this desirable end rapidly and without operative intervention is still awaited by those concerned with the relief of intestinal distention. The disadvantages in the use of long intestinal tubes are almost wholly concerned with the following factors:

1. Inadequacies of the design of tube and suction apparatus, and the technique of their use.
2. Delay in bringing about passage of the tube
   (a) from the fundus of the stomach to the pyloric antrum
   (b) through the pyloric sphincter into the duodenum
   (c) round the duodenum into the jejunum
   (d) down the intestine
3. Failure to recognize that operative intervention is imperative in those cases exhibiting impairment of blood supply of the bowel irrespective of the condition of the patient, and in certain other well-described circumstances.

It is the purpose of this paper to indicate the progress which has been made toward the goal of bringing about rapid decompression of the distended small bowel, and toward the reduction of the worry and detailed nursing care associated at present with the use of long intestinal tubes. Only when these have been achieved will a true evaluation of so-called conservative decompression of the small bowel be possible.

A perplexing number of different modifications, both in the technique of use and in the design of the long intestinal tube, have appeared in the literature, each claiming to improve by simplification the technique of intestinal intubation. Some designers claim uniformly good results and others appear to be more modest. This enthusiasm in claiming an easy solution to the very obstinate clinical problem of introducing a tube into the distended bowel and

These researches were supported by The Donald P. and Marion S. Ordway and the Augustus L. Searle Funds for Surgical Research.

Senior Research Fellow, United States Public Health Service.

Acknowledgment is made to the American Anode Company, Incorporated of Akron, Ohio for materials and technology of Latex Dipping.

removing the contents in all cases where this is desirable is probably not willful optimism on the part of the sponsors but is more likely due to a lucky initial run of cases or to an unconscious selection of less severe degrees of distention. These errors were anticipated and publication of results was purposely delayed until a suitably large series of cases had been collected. The first twenty cases in which the gravity director head[3] (a thin flaccid sack partially filled with mercury attached terminally to a suitably designed tube) was used were very encouraging. All the tubes were passed in an average time of 57.2 minutes from the nose to x-ray evidence of the tube in the second part of the duodenum. There were no failures to intubate the duodenum or to decompress. The cases covered most of the causes of intestinal distention but none of them were of very prolonged duration prior to intubation. As the series progressed, difficulties began to be encountered which called for re-application to the problem and further designing in order to try to overcome them. In my opinion, no entirely satisfactory long intestinal tube has yet been produced commercially. This delay is in part due to manufacturing difficulties caused by recent world events and in part to lack of a full appreciation of the requirements of a long intestinal tube.

Since the introduction of the hospital-fabricated intestinal tube,[4] considerable experience has been obtained in the design and use of the long intestinal tube. This has been achieved by building up tubes of various materials and designs, and in this way it has been possible to arrive comparatively rapidly at a satisfactory tube, clinically tested, which has as many of the desirable qualities as are at present possible. Further development is in progress and it is hoped that the subject matter to follow may be of help to those interested in the problem of rapidly decompressing the distended bowel and may serve to clarify some of the confusion which has arisen in connection with long intestinal intubation.

Before considering the design of long intestinal tubes, it is necessary to have a clear idea as to the conditions in the abdomen under which the tube may be expected to perform. By following the techniques and using the apparatus described by me,[5] it will be found possible rapidly to deliver the tip of the tube to the pylorus in all cases where no organic obstruction exists. By rapidly is meant in a matter of minutes with the aid of fluoroscopy. The rapidity of passage of the tip of the tube through the pylorus into the second part of the duodenum will depend upon favorable conditions, the ones which at present influence the design of the tubes, being:

1. The tortuosity and position of the outlet of the stomach
2. The presence of emptying waves of the pylorus sufficiently strong to carry the tube tip into the duodenum
3. The patency of the outlet of the stomach

The passage of the tube around the duodenum will depend upon factors similar to those to be described herein for the intestine, with the exception that occasionally some extra care has to be exerted in the management, owing to the tendency for reverse waves to occur in the first part of the duodenum.

RAPIDITY OF DECOMPRESSION

Delay at the ligament of Treitz is said to occur occasionally. This difficulty has been encountered only rarely so far. Once in the jejunum, the speed and maintenance of decompression will depend upon the cause of the distention, upon the design of tube and suction apparatus, and upon efficient management.

THE CAUSES OF DISTENTION

The exact causes of failure of function of the bowel which lead to distention are still obscure, though the conditions under which distention will occur are well recognized. It is beyond the scope of the subject of this paper to go into this matter except in so far as the design of tubes and their management are concerned. In simple mechanical obstructions where there is no intraperitoneal or neuromuscular abnormality, the postdecompressive function of the gut concerned with bringing about migration of tubes is maintained for a considerable time in spite of previous distention, so that almost as soon as a segment of gut in which the tube lies is emptied the gut is able to act upon a bolus and thus progressively decompress itself. The rapidity of emptying of the local segment of gut will depend upon the adequacy of the suction lumen relative to the length of the suction tube, the design of aspiration orifices, the viscosity of the intestinal contents, and the efficient maintenance of the patency of the suction lumen and suction apparatus during decompression. In this type of case, especially where distention of the gut has been of gradual onset, considerable hypertrophy of the musculature of the gut wall occurs, so that often the tube will be pulled into the patient without assistance by the medical attendant. It is in these cases that the most rapid decompression is achieved.

In cases where the postdecompressive function of the bowel is impaired or absent, from causes at present often known or sometimes obscure, progress of the tube down the bowel will depend even more upon careful attention to both the design and management of the tube and suction apparatus. As before, the rapidity of emptying of the local segment of gut in which the tip of the tube lies will depend upon the factors mentioned previously, but after the segment of gut in which the aspirating portion of the tube lies has been emptied, the bowel does not seem to recover its propulsive ability so quickly. Here the speed of decompression will depend upon the underlying cause of the bowel dysfunction, but the most rapid decompression possible will be assured by attention to the factors just mentioned. It is in these cases that the importance of efficient design and management should be most appreciated.

In clinical practice the impression has arisen that cases of pure adynamic ileus cannot be decompressed by means of a long intestinal tube. So far in some 250 cases of all types of bowel distention, where attention has been paid to efficient removal of intestinal contents and the prevention of redistention, no cases of pure adynamic ileus have failed to respond. In practice it has been found that from forty-eight to fifty-two hours may be required to achieve decompression in these cases, as opposed to twelve hours or less for obstructive cases with good postdecompressive bowel activity. Good nursing attention is necessary to insure that slack is continually present in the stomach where bowel function is impaired.

THE PROBLEM OF MAINTAINING DECOMPRESSION

As the tip of the tube travels down the gut, redistention may occur proximally in conditions where the bowel, once decompressed, is still unable to propel accumulated contents caudally. Where there is good bowel function after decompression, is in the simple mechanical obstruction of insufficient duration to impair postdecompressive propulsive ability of the bowel, and especially where hypertrophy of the bowel wall has occurred, redistention is not possible providing the intestinal tube is functioning correctly, since the gas and secretions will be carried from the upper gut down to the region of the aspirating portion of the long intestinal tube, there to be removed. Where the postdecompressive function of the bowel is faulty in respect to both absorption and propulsion of contents, redistention of proximal bowel will occur after the aspiration section of the tube has traveled on. The management of this situation will be discussed later under the heading "Aspiration Holes." With these considerations in mind the desirable qualities of a long intestinal tube should be examined.

THE IDEAL LONG INTESTINAL TUBE

Materials.—

The *tube* should be:

(1) Nonirritating to the nasal passages and oropharynx
(2) Glassy smooth inside and out
(3) Of high tensile strength
(4) Unaffected by intestinal contents even after prolonged contact with them; that is, should not stain, stiffen, or pick up irremovable intestinal odor
(5) X-ray opaque.

Any attached *thin sacks*, that is, balloons or noninflatable sacks, with or without mercury, should be constructed of a material that is:

(1) Water repellent
(2) Impermeable to gases
(3) Of the highest tensile strength
(4) Unaffected by mineral oil
(5) As durable as the tube.

CONSTRUCTION OF THE IDEAL LONG INTESTINAL TUBE

The tube should be usable in all types of cases from infants to the aged in any clinical condition with regard to the distention and its consequences.

Suction Tube.—

Flexibility: The tube should have maximum flexibility in order to be able to negotiate the sharpest curves and in order to cause the minimum resistance to any available propulsive capacity of the gut, and at the same time be easily introduced into the nose and stomach.

Wall: The wall should be so designed that occlusion of the lumen of the tube cannot occur when the tube is bent acutely or twisted (Fig. 14).

Lumen: The lumen of the suction tube relative to its length should be of adequate size to provide, with a minimum of nursing attention, constant and rapid removal of intestinal contents when maximum constant suction is applied as they come within reach of the aspiration orifices.

Aspiration orifices: The aspiration orifices should provide for adequate removal of intestinal contents without blocking and should in no way weaken the tube so as to cause obstruction upon twisting or kinking at the point of perforation. They should be so designed that the lining membrane of the gut cannot be sucked into them.

Length: The length of the tube should be as long as is necessary to perform its function efficiently. The longer the tube, the more resistance there is to the flow of contents within.

Outside diameter: The outside diameter should be held to the smallest possible dimensions while fulfilling the foregoing conditions.

Inflation Tube or Tubes Where Used.—The inflation tubes should be attached or incorporated into the suction tube in such a way that replacement of balloons and attachment of connecting pieces are simple and trouble-free. The lumen should be sufficiently large to permit of easy gas flow.

Connecting Pieces.—The pieces connecting the suction lumen to the suction apparatus should be simple and of the same bore throughout as that of the suction tube and so arranged in the case of multilumen tubes that confusion is avoided as far as possible.

Cost.—The tube should be so designed that cheap production is possible and so that it can be supplied for use finished and tested to precise limits by the manufacturers in order to avoid faulty assembly by unskilled personnel. If expensive, the tube should be usable for two or more intubations before scrapping. Any replaceable expendable parts should be designed so as to minimize the skill required to fit them, and if this is impossible, return of tubes to the manufacturer for servicing is to be desired.

Clinical Use and Management.—Where used to relieve intestinal distention, the ideal tube should be capable of rapidly effecting and maintaining decompression of the distended bowel from whatever cause; that is, it should be capable of rapid and certain introduction with a minimum of strain on the patient, through the nose or mouth down the esophagus, through the cardia, into the fundus of the stomach, across the stomach to the pyloric antrum, through the pyloric sphincter, around the duodenum, past the ligament of Treitz, and on into the small bowel. Once there, it should rapidly bring about decompression of the bowel, whatever conditions are prevailing in the abdomen. It should decompress the distended bowel whether the distention is due to neurogenic dysfunction, to irritation of the peritoneum, to a mechanical obstruction, or to a mixture of these three causes. Whether the mechanical obstruction is single, closed loop (multiple or single), simple, or strangulating. In postoperative distention, it should be capable of passing kinks formed by postoperative fibrinous bands or by fibrous adhesions.

Where the cause of small bowel distention is in doubt, the tube should be so constructed that the bowel can be sealed off promixally by means of a balloon, so that radiopaque material may be forced distally to reveal any possible cause

of distention on the basis of obstruction. Where a bolus is arrested it should be so constructed that the bowel can be sealed proximally and gas injected distally in order to unkink the bowel or to break down adhesions. At operation where the gut is distended, the tube should be so constructed that a balloon can be inflated in order to facilitate manipulation of the tube through the bowel wall for the purposes of decompressing the bowel.

Simplicity of technique and management is essential. Complicated and skillful manipulations are to be avoided, and the minimum of special nursing care is desirable.

Available Materials for Tubes.—Natural rubber has long been in use for the construction of tubes used in the practice of surgery. More recently mixtures of natural and synthetic rubbers have come into use. Most tubes made from these materials contain irritating chemicals which cause a reaction of the mucous membranes with which they come into contact. This reaction may merely cause discomfort of varying degree to the patient, or may be in part or wholly responsible for complications such as severe pharyngitis or edema of the glottis, particularly in debilitated patients. Rubber tubes can be made very flexible, which is to be desired, but their elastic property is not required. The surface of these tubes is relatively rough even with treatment by waxes, since these quickly wear off in use. Rubber tubes pick up an unpleasant smell which is almost impossible to remove. They also stain badly in use. They can, however, easily be made radiopaque. Little development has been made toward removing the undesirable qualities of rubber used in intestinal tubes. Tubes made of pure natural latex tend to have a high water absorption and are too soft.

Recently great strides have been made in the development of rubber-like plastic materials, and these materials are still under continuous development. The method of building up tubes mentioned previously has greatly facilitated the clinical testing of the most promising types described here.

1. *Silicon rubber:* Silicon rubber, is entirely inert chemically, is difficult to fabricate, and has a rough surface similar to that of rubber. It lacks one very important property, namely tensile strength. This defect could be compensated for by the inclusion of a metal wire in the wall of the tube running longitudinally, but at present it is not possible to obtain this form of construction.

2. *Polyethylene or polythene:* Polyethylene, is a pure waxlike plastic. It is very smooth and inert but is too stiff in the sizes required for intestinal tubes, and at present it cannot be satisfactorily softened by addition of softening agents. It has a tendency to split when bound onto metal inserts. It has a poor resistance to "cold flow."

3. *Polyvinyl resins:* The most satisfactory material at present available is the polyvinylchloride type of resin. These resins are hard in the pure state and have to be softened for fabrication with plasticizers which do not enter into chemical combination with the resin but are mixed with it reversibly. Commercially the softening agents, or plasticizers, are blended with the resin according to the purpose for which the material is to be used. For medical purposes, toxicity and retention of plasticizer in the resin are the guiding considerations.

The basic resin is nontoxic, but the plasticizers may be toxic. Owing to the loose nature of the combination between resin and plasticizer there is a tendency for the plasticizer to leave the resin and thus cause a stiffening of the material. This phenomenom may occur very rapidly in the gut with improperly blended plasticizers so that a tube may be introduced into the intestine in a soft, flexible state and be removed with difficulty and discomfort to the patient in a much harder and stiffer condition. A product sold commercially as Koroseal surgical tubing has been found to be a very satisfactory material. It has nontoxic plasticizers blended into the basic resins of such physical properties that they do not tend to leave or leach out of the material quickly, so that a considerable life is obtainable from tubes constructed of this material. This material should not be boiled, as this will accelerate leaching. Koroseal has the advantage of being transparent when first put into use, so that the color of aspirated contents can be observed sooner than would be possible if the tube were opaque. However, it soon begins to stain in use, and gradually becomes darker and darker until discarded. This material is not markedly radiopaque but can be made so by the addition of platinum chloride. It can be seen clearly on Potter-Bucky plates and less clearly with a good modern fluoroscope without the addition of platinum chloride. The addition of platinum chloride as used in the Honor-Smathers tube still does not make the tube as brilliantly x-ray opaque as rubber tubes. Its surface is smooth but tacky as supplied. This tack can be removed by treatment with silicone oil as described in the section on the construction of a satisfactory tube. Silicone oil treatment also reduces the friction of the wall of the suction lumen and greatly facilitates the flow of intestinal contents therein. This material does not develop an objectionable smell as with rubber tubes. The intestinal odor picked up from the gut is easily removed. Another polyvinyl chloride type of tube called "Tygone" has been found quite unsatisfactory as it rapidly stiffens in use.

4. *Geon polyblend:* Another material of interest which has not yet been tested is a mixture of polyvinyl chloride and synthetic rubber, which bears the trade name, Geon Polyblend. It is claimed by the makers to be a very versatile material and to eliminate the difficulty of plasticizer migration, since the synthetic rubber used as a plasticizer is fixed and cannot be removed from the resin.

It is to be hoped that as soon as the requirements as to dimension, construction, and conditions of working of intestinal tubes can be made known to the plastic industry an entirely suitable material will be developed.

Materials for Attached Thin Sacks.—Pure natural Latex films have been used exclusively for the fabrication of the various design of bolus. Natural Latex films possess a very high tensile strength but are not as durable in use as could be desired, especially where they come in contact with mineral oil, and frequent replacement is required. These films are also permeable to gases, especially after absorption of water. This may lead to complications in use, since sacks made of natural latex may distend with gas when in the bowel unless precautions are taken to control this phenomenom. There is now an ever-increasing selection of latex-like film-forming materials becoming available to industry so

that in the future a more suitable material may emerge for this purpose. Neoprene and polyvinylbutyral show considerable promise.

CONSTRUCTION OF THE SUCTION TUBE

For the purpose of discussion the construction of the suction tube may be divided into the bore or lumen, the wall, and the outside diameter.

The clinical significance of an adequate lumen for rapid, trouble-free removal of intestinal contents of any viscositiy likely to be encountered has already been referred to. Practically, I have found that a bore of not less than $\frac{1}{8}$ inch in a tube 9 feet in length will fulfill the specifications. With an adequate wall thickness to prevent kinking, the outside diameter of a Koroseal tube of adequate flexibility comes to $\frac{7}{32}$ inch, or $\frac{1}{32}$ inch less than $\frac{1}{4}$ inch (Fig. 5, *No. 8*). The thinner walled Koroseal tube used by Herrera and co-workers[6] of $\frac{1}{8}$ inch bore and $\frac{1}{32}$ inch wall I have found to be unsatisfactory, as kinking occurs in the stomach if the tube is passed into the patient too rapidly. It is, however, a useful size for tubes to be used in children. This size should be carefully inspected for irregularities in the wall which will favor the formation of kinks, since the uniformity of the wall thickness is difficult to obtain in the manufacturing process. Koroseal, especially when treated with silicone oil (see section on Construction), is almost entirely free of irritation to the mucous surfaces of the nasopharynx and is much less irritating than rubber tubes. For reliable general hospital use the larger size is to be recommended.

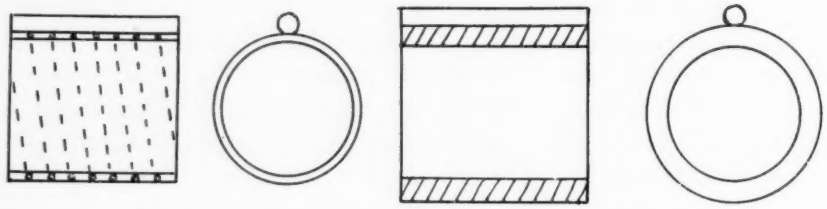


Fig. 1.—A comparison between the author's present design of tube and what may be achieved in the future. (*a*) Shows the tube with a spirally wound support thus permitting considerable reduction in the wall thickness without sacrificing the size of the lumen. (*b*) Shows the unsupported wall of Koroseal drawn to the same scale. The development of the supported wall tube is to be greatly desired, especially with regard to the use of the long intestinal tube in infants and young children.

The outside diameter of an indwelling nasal tube should be as small as possible after the minimum bore and wall thickness considerations mentioned have been taken into account. In practice the size of $\frac{7}{32}$ inch Koroseal tube will be well tolerated by most patients.

Consideration of these criteria will show that only reduction of the wall thickness is possible as the means of reducing the outside diameter of the tube. Since $\frac{3}{64}$ inch in an unsupported wall is the minimum practical thickness, it is logical that the only way in which reduction of the outside diameter of the tube is possible is by the inclusion of a flexible support in the wall. This can be done with a stiff, springy material, such as nylon or metal wire. By this means a tube of hitherto impossible very small outside diameter can be made

without sacrificing the bore, flexibility, or freedom from kinking. This type of construction, shown in Fig. 1, is under consideration at present.

CONSTRUCTION OF INFLATION TUBES WHERE USED

For experimental purposes during the development of the various designs of tube, up to two separate inflation tubes made of polyvinyl chloride have been used. At present it is difficult to obtain sufficiently fine tubes in Koroseal material, and so a resin-plasticizer mixture with less stable softening agents has been used. Here the stiffening from leaching out of plasticizer is not so important as in the case of the suction tube, since the tubes are of such a size as not to give trouble upon removal. These inflation tubes are replaced more frequently than the suction tubes. They are separate from the suction tube as in the original Miller-Abbott-Johnston tube, and in the final development of a satisfactory tube they will be incorporated in the suction tube in such a way as not to affect the efficiency of the suction lumen and also so as to simplify commercial production.

Aspiration Holes.—

1. *Size and shape:* Aspiration holes should be of maximum size possible without weakening the wall of the tube so that kinking or twisting will lead to obstruction at the point of perforation (Fig. 14). Elongated or oval holes, provided adequate support is given, are advantageous.

2. *Number and position of holes:* Much confusion has arisen over the question of the number and position of aspiration holes. There is a fundamental difference between the method of working of an inlying or static gastroduodenal tube of the Wangensteen type and a migrating or dynamic, bolus-tipped long intestinal tube. It has been found that two full-lumen, elongated holes, diametrically opposite each other, supported by a metal insert and placed near to the tip of the tube just distal to a balloon (Fig. 2, *a*), have many advantages over any other possible arrangement, and are responsible for the superior results which seem to attend its use in so far as rapid delivery of the tip of the tube to the pylorus and the rapid decompression of obstructed cases, and the more certain though slower decompression of cases of adynamic ileus, are concerned. The disadvantages of this arrangement of holes can be easily overcome. Various types of tubes with regard to the position and number of aspiration holes have been tried. The advantages of the terminal hole system mentioned previously appear to outweigh those of the multilevel hole system in practice. Although holes proximal to the balloon may be thought desirable, the fundamental object of the tube must be borne in mind, namely, the rapid introduction into and the rapid progression of the tube down the bowel, and this, in my opinion, can at present be achieved only by the terminal hole arrangement. The terminal holes are sucking at the most distal point of the tube and are held in the lumen of the gut by the distended balloon bolus, situated just proximal to the aspirating point. Suction can take place only at these holes. Should blocking of the tube be suspected, irrigation of the tube will clear these holes and these holes only, so that the point of suction at the most distal point of the tube possible is assured at all times during decompression. Furthermore, multiple-hole systems cannot

be used with maximum constant suction, since after the gut has been emptied locally the mucosa becomes sucked into the holes if large enough to be efficient, and will grip the gut wall very effectively, thus fixing the tube in the bowel and hindering, if not preventing, migration. With this type of tube a suction apparatus requiring alternate suction and injection is essential if constant nursing is to be avoided. This point is shown graphically in Fig. 2, *b*.

The terminal holes situated in front of the balloon bolus are very desirable when it is desired to inject a little barium sulfate distal to the balloon bolus inflated sufficiently to block the bowel proximally. This is not possible with any of the existing designs of tube. The most important reason for this position of the holes concerns the technique of introduction of the tube. It is often possible in the severer grades of distention to get only the tip of the tube into the stomach.[5] In order to advance the tube rapidly to the pylorus, it is often necessary to inject gas into the stomach. This becomes impossible with a multilevel hole system. (See section on Technique.)

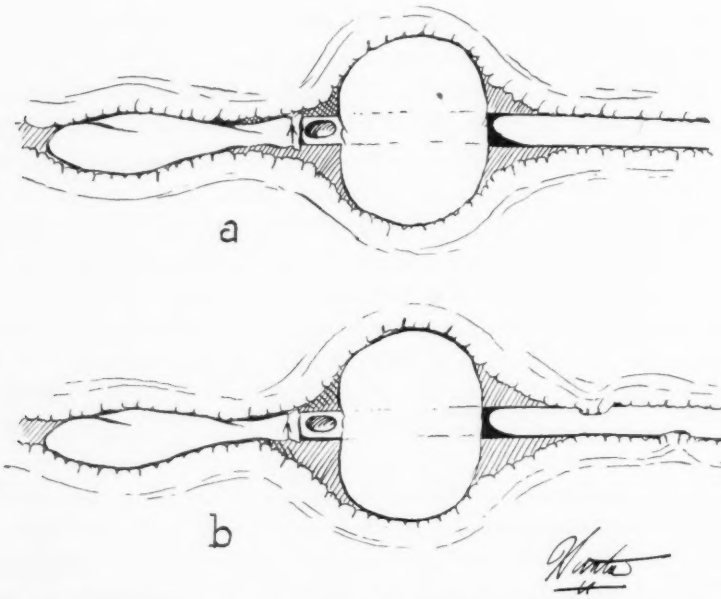


Fig. 2.—The advantages of the terminal holes placed just distal to the balloon. (*a*) Shows the balloon holding the gut wall away from the aspiration holes. Maximum continuous suction can be maintained in front of the balloon at all times during decompression. Should blockage occur, clearance of the holes distal to the balloon by injection of liquid is assured. Thus, the most rapid possible decompression is achieved. The importance of this arrangement in the rapid delivery of the gravity head to the pylorus and in the blocking of the bowel proximal to the holes is mentioned in the text. (*b*) Shows a tube with holes proximal to the balloon. Maximum continuous suction cannot be used efficiently since the lining membrane of the bowel will become attached to the tube and offer considerable resistance to advance of the balloon relative to the bowel length. Intermittent suction would avoid this, but the other disadvantages of this system mentioned previously and in the text do not, in the author's opinion, warrant its use.

3. *The problem of maintaining decompression:* The possible disadvantages of the terminal hole system are concerned with two considerations, the inability to keep the stomach empty while the tube is passing from the pylorus into the duodenum, in cases where delay occurs at this point, and the maintenance of

decompression where the postdecompressive propulsive function of the intestine is impaired.

The latter problem is common to all long intestinal tubes, with the possible exception of the arrangement of holes suggested by Cantor.[7] In the case of delay at the pylorus, it is sometimes found that the terminal hole arrangement will not keep the stomach empty when the tube comes to lie in the region of the pyloric sphincter and that intestinal contents regurgitate back into the stomach past the aspiration holes. If holes are placed so as to lie in the stomach when the tip of the tube is lying in the pylorus, the stomach may be kept empty, but as soon as this is done the advantages of the terminal holes placed in front of the balloon are lost, and it is found in practice that the more distal holes of a multilevel hole system tube tend to block because of the reduction of flow through these holes occasioned by a diminishing gradient of negative pressure from the most proximal hole distally. Once the terminal holes become blocked, in a multilevel hole system, they cannot be cleared by irrigation since a sufficiently high pressure cannot be brought to bear on these holes in the presence of patent proximal holes. Further, under these conditions where a balloon bolus is used, the balloon bolus when inflated tends to obstruct free flow of the intestinal contents to the aspiration holes situated proximal to it. The presence of holes proximal to a balloon bolus also makes local bowel study with radiopaque media more difficult, since spillage of the media occurs through the proximal holes. Also, the technique of overcoming kinks due to fibrinous band adhesions by air injections, mentioned previously, is not possible in a multilevel hole system.

In the case where the propulsive function of the intestine is impaired, the type of multilevel hole tube introduced by Cantor in which a group of holes are cut so as to come to lie in the stomach and thus keep the stomach empty and prevent redistention does not overcome the difficulty. If the holes are cut so as to come to lie in the stomach when the tube is swallowed and with the tip of the tube lying in the jejunum, they will prevent redistention only as long as the tube is prevented from traveling, in which case the object of progressive decompression of the bowel is defeated. On the other hand, if the holes are cut after the tip of the tubes has migrated down the bowel, redistention may have already occurred. As has been mentioned, these proximal holes will also greatly reduce the efficiency of the more distal groups of holes near the tip of the tube. Where there is good propulsive function of the gut, multiple holes are unnecessary. Where the propulsive ability of the gut is impaired, considerable delay or even failure in decompression may occur, due to the lack of suction at the most distal point of the tube, since the proximal aspiration holes will tend to reduce or even obliterate the negative pressure around the terminal holes. Also, the limpet-like effect shown in Fig. 2, *b* will introduce still more resistance to migration of the tube. Thus, at best this system will give the same end result as the introduction of a separate inlying gastric tube at the expense of continued intestinal decompression, providing that the upper group of holes remains in the stomach. However, as soon as they move into the duodenum or jejunum a high

intestinal fistula is produced since the upper intestinal juices will be removed and not allowed possibly to pass down the decompressed bowel to be removed at the tip of the tube. Therefore, any possibility of absorption is precluded.

THE SOLUTION TO REDISTENTION

An inlying gastric tube, so placed with certainty in the fundus of the stomach as to exclude swallowed air from the gastrointestinal tract and as far as possible to minimize the loss of upper intestinal juices, would seem to be a better way of preventing redistention and of keeping the stomach empty should this be necessary, without impairing the efficiency of the long intestinal tube.

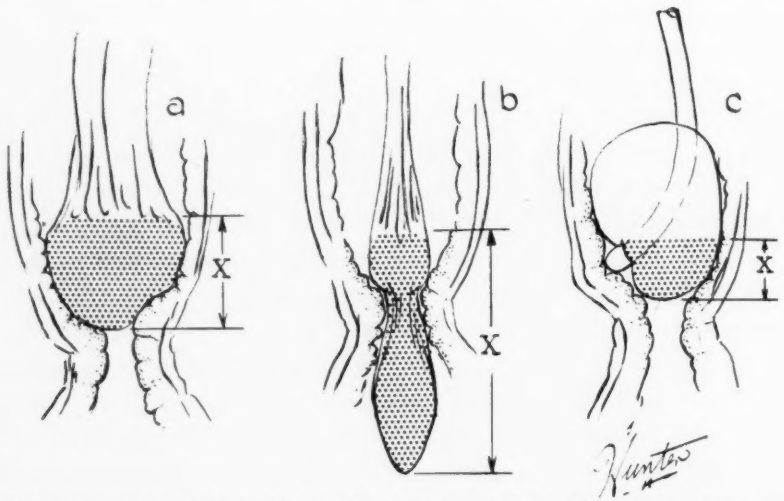


Fig. 3.—A comparison between the mode of action of the various types of mercury-loaded attachments. (*a*) Shows the Honor-Smathers and Cantor type of gravity director head with the blunt end. Attention to the heights (*x*) will show that the weight of mercury acting on the lowermost portion of the gravity director head is greatest with the author's pointed design shown at (*b*). This is probably of great importance in negotiating narrowed portions of the alimentary tract, particularly the cardia. (*c*) Shows a mercury-loaded balloon attached around the aspiration tube near its tip as with the Miller-Abbott, Harris, and Kaslow long intestinal tubes. Reference to Fig. 4 will show what can happen when the protruding tip becomes arrested in the esophagus.

Bolus Design.—The original Miller-Abbott-Johnston tubes were fitted with a tied-on condom which was inflatable by a separate small tube passed along with the main suction tube. It was found that this inflatable bolus was a very efficient mechanism for enabling the gut to act upon and bring about migration of the long intestinal tube attached. It was also found that the balloon bolus stimulated the gut as stretching occurred and that, if the balloon bolus was left inflated for any length of time without permitting travel, damage would occur to the gut wall from impairment of its blood supply. In 1942, Sivertson suggested to Wangensteen the use of mercury to be introduced into the balloon of the Miller-Abbott tube after it had been swallowed by the patient. It was thought that this would greatly aid the passage of the tip of the tube through the pylorus and into the intestine. Harris[8] reported a series of cases in which this technique was used. At this time, finding the commercial so-called Miller-Abbott double-lumen tubes in England unsatisfactory, I took to fabricating tubes by assembly from easily obtainable parts, with features which seemed to be more likely

to succeed in rapid decompression of the distended human intestine. Unaware, at the time, of Sivertsen's suggestion, I decided against the placing of mercury in the balloon of the fabricated tubes of the original Miller-Abbott type and in favor of a thin, flexible sack attached terminally to a modified balloon bolus tube. It seemed more logical to apply a mass to be acted upon by gravity terminally, so that as the mass advanced it would drag the tube after it instead of along with it as in the case of the mercury-weighted balloon bolus. This arrangement also gave more scope for variation in shape and eliminated a projecting tip which might be arrested at any of the restricted portions of the upper gut, such as the lower end of the esophagus or the pyloric canal (Figs. 3 and 4).

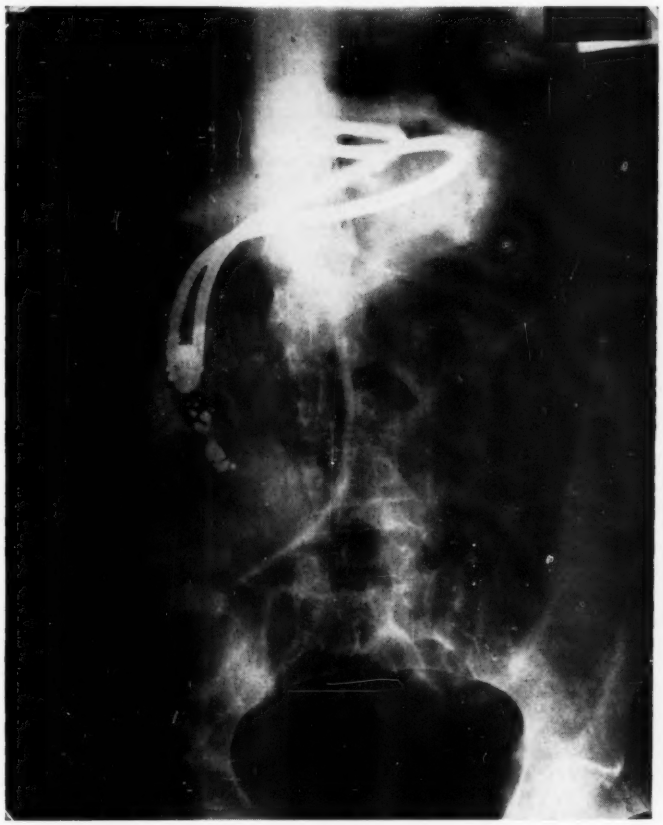
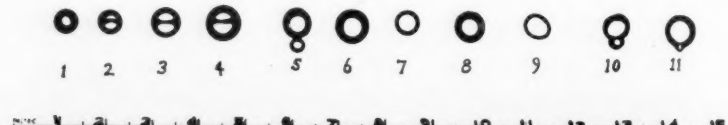


Fig. 4.—A radiograph of a so-called Miller-Abbott double-lumen tube in which mercury had been used in the balloon. Arrest of the tube in the lower end of the esophagus as shown diagrammatically in Fig. 3, *c* can be seen. The tube has passed double into the second part of the duodenum.

It seemed logical also to utilize the fluent properties of the mercury. The flexible sack, therefore, was only partially filled with mercury, leaving no air space above the mercury, thus allowing the mercury to flow unimpaired, yet keeping it at the same time completely harnessed. A further advantage of this arrangement was the ease with which it could be introduced into the nose, providing the sack was properly designed, and the ease with which the tube would pass down

into the stomach after swallowing as compared to the subsequent addition of mercury to the balloon of a Miller-Abbott tube after passage into the stomach. In an attempt to simplify the technique of intestinal intubation, Harris eliminated an inflatable bolus and produced the first recorded single-lumen long intestinal tube, following his observation that the mercury-filled balloon of a Miller-Abbott tube would travel down the gut without inflation.[9] Subsequently, Cantor[7] utilized a partially filled sack of mercury attached terminally to a single-lumen tube of rubber with a larger bore (Figs. 5 and 6). Soon after the introduction of the hospital fabricated tube fitted with a gravity director, plastic tubes



RUBBER TUBES		Suction Tube Diameter (Inches)		Catheter Size F Approx.	
Number	Name	Inside	Outside	Inside	Outside
1	Harris	.076	.173	7	13
2	So-Called Miller-Abbott Double-Lumen Tube	.079	.173	6	12
3		.086	.213	8	14
4		.110	.254	8-9	18
5	Wild	.120	.204	10	15
6	Cantor	.141	.240	12	18
PLASTIC TUBES					
7	Wild	.129	.180	10	14
8	Wild	.129	.221	11	17
9	Kaslow	.150	.189	11	14
10	Wild	.136	.201	10	15
11	Honor-Smathers	.157	.228	11	17

Fig. 5.—A comparison between actual cross sections of long intestinal tubes. It will be noticed that only the largest size of so-called Miller-Abbott double-lumen tubes (No. 4) has anything approaching an adequate suction lumen. No. 5 shows the author's early black catheter-rubber double tube. No. 7 shows the cross section of an early polyvinyl chloride plastic tube commercially produced as radio spaghetti used by the author. This was plasticised with tricresyl-phosphate and was as irritating to mucous membranes as rubber. The plasticiser also leached out, leaving a stiffer tube. However, the suction lumen was adequate and kinking did not occur in spite of the thin wall, since the tube was much less flexible than those at present recommended. No. 8 shows the Koroseal surgical tube which the author is at present using and which avoids the difficulties concerned with the function of efficient aspiration of the long intestinal tube. No. 9 shows the inadequacy of wall thickness of the Kaslow tube. No. 10 shows a crude commercial double extrusion attempted in England during the recent world conflict. The author was unable to use this owing to the inaccuracies of the section. No. 11 shows the excellent double extrusion of the Honor-Smathers tube. The inflation tube is too small and cannot be peeled off from a suction tube; special fittings which give rise to troubles must be used.

which were a great advance over rubber became available, and, at the same time, the method of tying on the balloon bolus shown in Fig. 7 enabled the tubes to be passed nasally.

The Design of the Gravity Director-Head.—In the initial experiments, I used finger cots, plain-ended condoms, and severed fingers of surgical gloves, together with varying weights of mercury and with air completely expressed before tying on. The distance of the gravity director-head from the tube tip was also varied. The finger cot and the condom were considered too thin for general use and for safety because of the danger of rupture during passage into or re-

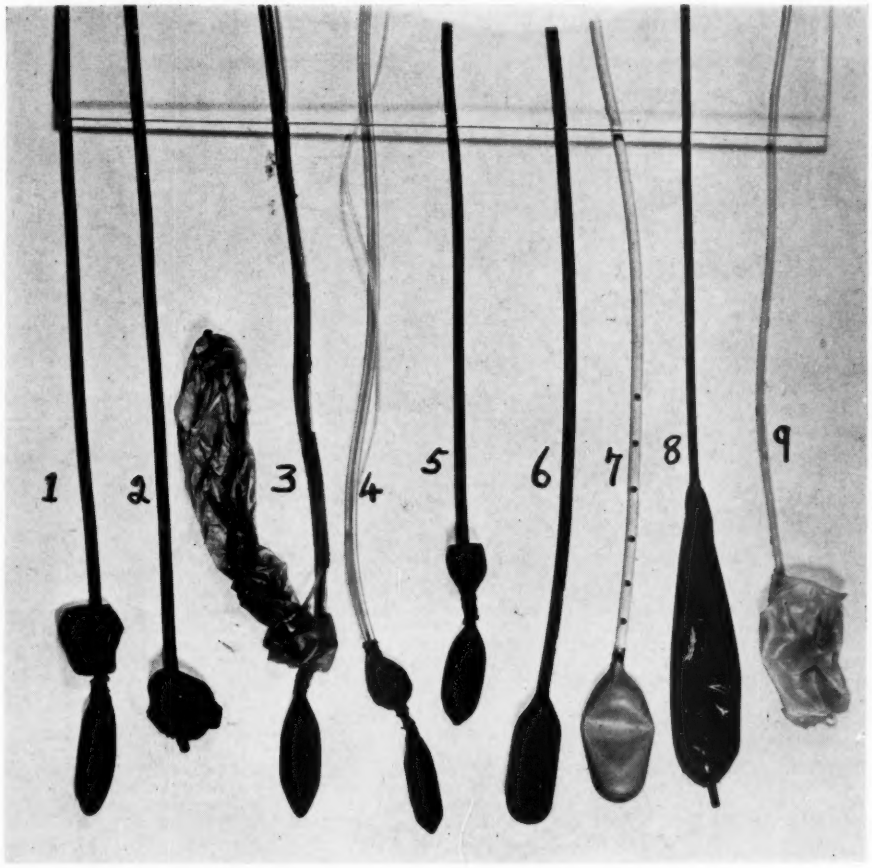


Fig. 6.—A comparison between various designs of long intestinal tubes. No. *1* shows the author's modification of the so-called Miller-Abbott double-lumen tube. There are no suction holes proximal to the intestinal balloon. The holes are situated between the balloon and the gravity director head and are supported by a metal insert to which is attached the gravity director head. No. *2* shows a standard double-lumen tube, before modification for comparison. No. *3* shows the author's gastric balloon tube built up in the same manner as the true Miller-Abbott-Johnston tubes. Notice the binding of the three tubes to prevent tangling. The gastric balloon is attached as near to the intestinal balloon as possible. No. *4* shows the author's present standard built-up tube with the combination balloon and gravity director head designed for convenient production. No. *5* shows the author's modification of the Honor-Smathers tube. A cross section similar to No. *5* of Fig. 5 is to be desired ultimately. No. *6* shows the Cantor rubber tube with the large, blunt-ended gravity director head. The two groups of holes extending for some distance proximally can just be seen. No. *7* shows the Honor-Smathers plastic tube. This has a large, blunt-ended gravity director head which can be inflated. No. *8* shows the Harris tube. No. *9* shows the Kaslow tube.

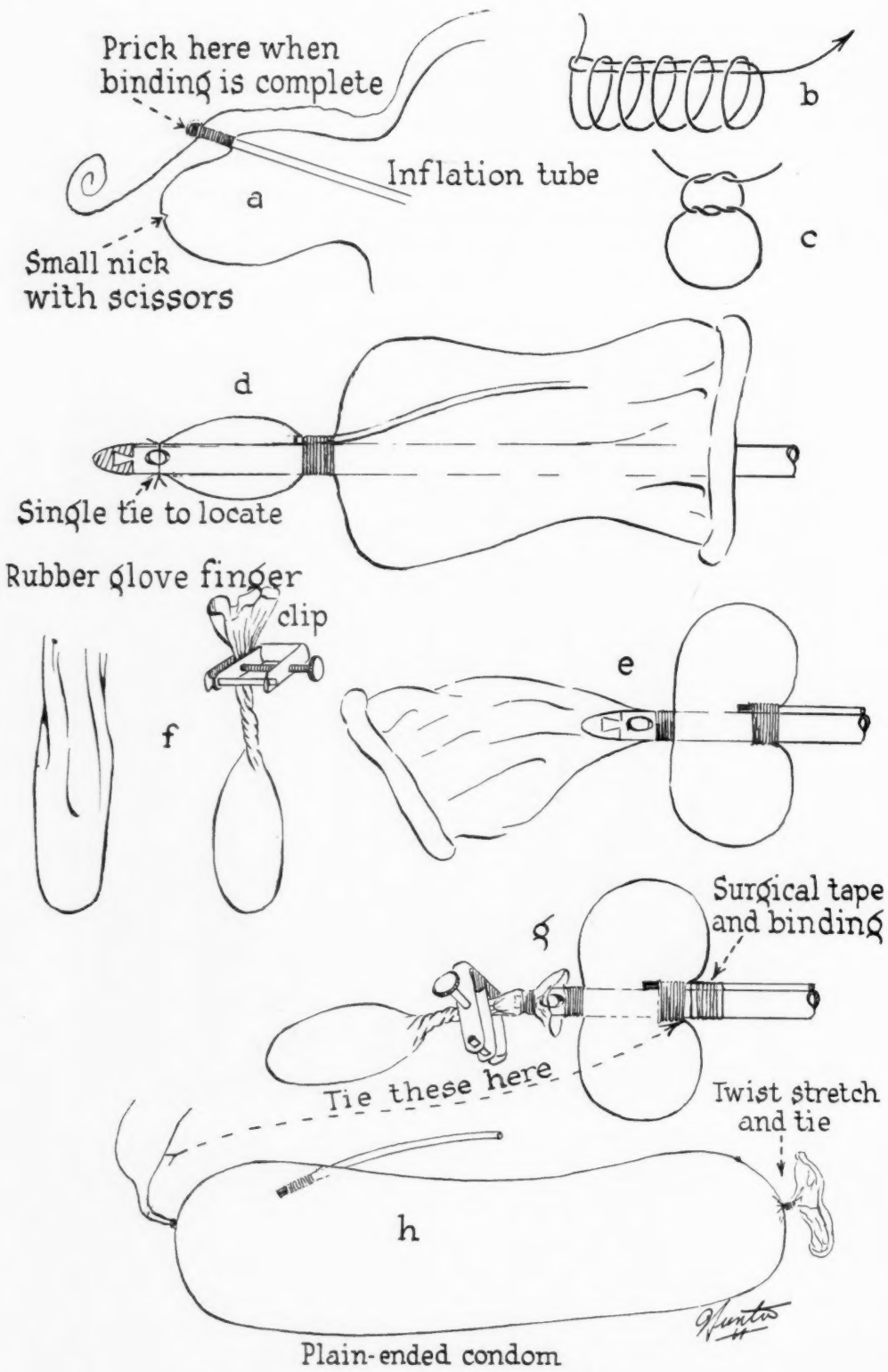


Fig. 7.—*(For legend see opposite page.)*

moval from the nose with consequent aspiration of mercury into the lungs. It was found that the thicker finger-shaped sacks fabricated from surgical glove fingers were just as good as the thinner types. Further, it was found that after prolonged stay in the intestine they did not distend by diffusion of gas sufficiently to cause impairment of blood supply of the intestinal wall or to prevent easy

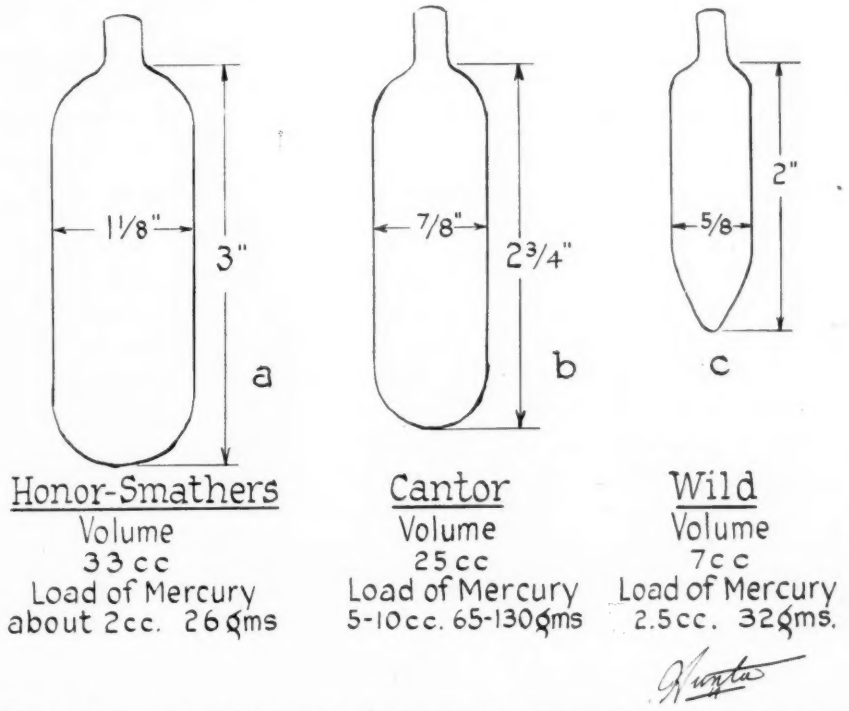


Fig. 8.—A comparison between the various types of gravity director heads. It will be seen that the author's design (*c*) is the smallest and that it is somewhat pointed. The advantages claimed for this design are: (1) Easily introduced into the nose without instruments thereby eliminating danger of breakage and spillage of mercury into the lungs. (2) Easily withdrawn through the nose even if it should distend in the gut after prolonged intubation. (3) Easily withdrawn through a stenosed portion of the alimentary tract should it pass through. (4) Passes easily through the lower end of the esophagus into the fundus providing the proper technique is carried out. (5) Brings the greatest possible weight of mercury to bear on the tip.

Fig. 7.—The attachment of the teat-ended condom to the fabricated tube shown in Fig. 11. (*a*) The inflation tube is fitted with a needle insert with edges carefully filed smooth. Then this tube is pushed through the teat as shown and multiple ties are carried out as shown at (*c*) doubling back and forth. The airway is pricked (this should not be forgotten) and a small nick made with scissors in the end of the teat. (*d*) The fabricated tube is slipped into position and a locating tie is made over the holes as shown. The inflation tube is loosely whipped with the loose ends shown at (*a*) in order to locate it and the tube and to hold the tip parallel with the aspiration tube. (*e*) The condom is turned back on itself and whipped (as shown at *b*) in position exactly over the metal insert. It is important not to miss or the plastic will give and obstruct the lumen. Surplus rubber is carefully cut away without nicking the balloon, and the balloon is inflated and tested under water. The capacity of the balloon should be 15 to 20 c.c. and doughnut-shaped as shown. (*f*) The little finger of a No. 7 or 8 surgical glove is loaded with 2½ c.c. of mercury and screwed up to exclude all air and a screw clamp applied. (*g*) The gravity director head is tied in place with strong silk by multiple knotting shown at (*c*). Surplus rubber is trimmed off and the screw clamp removed. The gravity director head is tested by pressing the mercury load up against the binding and observing for leaks. Surgical tape is applied and whipped on lightly to hold it in place when in the bowel. This securely anchors the inflation tube. (*h*) If desired, a gastric balloon, fabricated from a plain-ended condom as shown, is attached as near to the balloon as possible. It is extremely important to bind the three tubes together at intervals for 12 inches to prevent tangling. This can be done with adhesive tape and binding, which should not be too tight since no metal inserts are present to insure patency of the lumina. The finished balloon should be dusted with talc and the tube stored in a box away from direct sunlight.

removal through the nose. Harris has drawn attention recently[10] to the danger of distention of his full-sized condom sacks and has suggested the method of avoiding this by flushing out the condom with carbon dioxide before making the final tie. Cantor at first used plain-ended condoms but subsequently designed a gravity director head having a volume of 25 c.c. which contained 5 to 10 c.c. of mercury (Fig. 8). This size is dangerously large in view of the distention problem unless carbon dioxide flushing or neoprene is used. Neoprene also has the advantage of being oil-resistant but has a high chlorine content which, upon reacting with mercury, may be of serious consequence. Reference to Fig. 3 will show that there is one more advantage of the finger-shaped gravity director

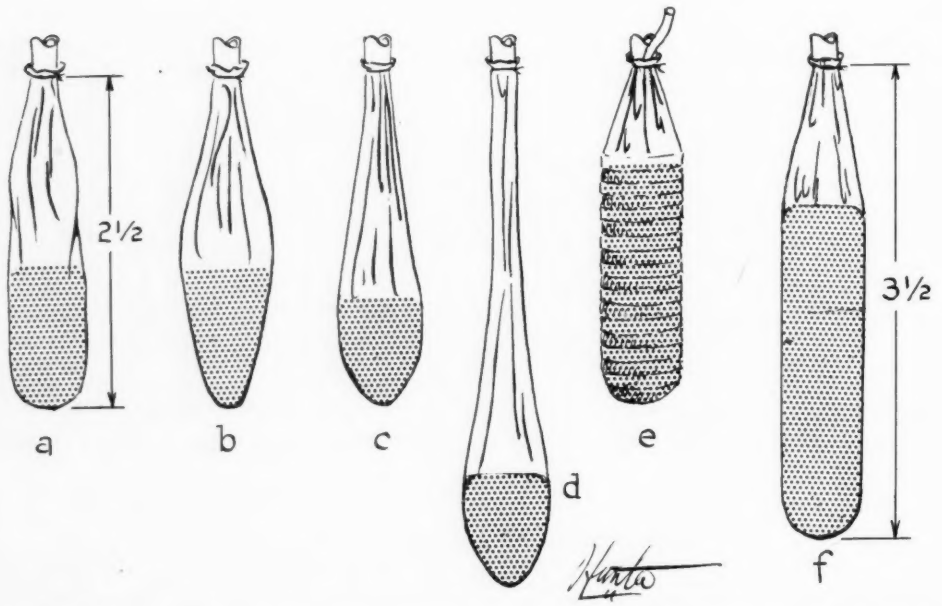


Fig. 9.—A comparison of various gravity director heads used by the author besides the Honor-Smathers-Cantor types. (*a*) Shows the small finger of a No. 7 surgeon's glove. The others were fabricated by the author from latex. (*b*) This shape was found to be too pointed and to have too great a tendency to enter the trachea, especially in old people. (*c*) Shows the present design loaded with mercury. (*d*) Shows a longer one which it was thought might facilitate passage through the pylorus. (*e*) Shows an expansible type which would lengthen somewhat on inflation. An intestinal balloon was not used with this type. (*f*) Shows a useful type for dilating stomas in postgastrectomy distentions. This has a load of 120 Gm. of mercury and is passed orally.

head over the blunt-ended condom shape in that the weight of mercury concentrated at the tip is considerably greater than with the same amount or more of mercury placed in the condom. This is probably an important factor in bringing about an unimpeded flow through the cardia and pylorus. Fig. 9 shows various shapes and sizes of gravity director-heads tested. No advantage seems to be gained by using more than 3 c.c. or 40 Gm. of mercury. The best volume and shape is shown in Fig. 8, *c*. This is slightly more pointed than a surgical glove finger but not so pointed as the one shown in Fig. 9, *b* which shows too great a tendency to enter the trachea. The advantages claimed for this shape and size are:

(a) Easily introduced into the adult nose without forceps and easily removable through the nose even if distended with gas after prolonged stay in the intestine.
(b) Greatly facilitates swallowing of the tube and makes possible the easy introduction of a very limber tube into the stomach
(c) Shows no tendency to arrest at lower end of the esophagus (Figs. 3 and 4)
(d) Can be rapidly delivered to the pylorus in practically all cases under fluoroscopic control
(e) Can often be manipulated by alteration of the position of the patient through the pylorus into the duodenum and round the duodenum to the ligament of Treitz under fluoroscopic visualization.

Early in the clinical evaluation of the gravity director-head I used single-lumen tubes of adequate bore similar in design to the tube described by Cantor.[7] Upon passage down my own gut without suction I found that with 60 Gm. of mercury instead of the 70 Gm. suggested by Cantor in a gravity director-head made from a blunt-ended condom, the rate of travel down the gut from the duodenum to the ileocecal valve as judged by radiography was considerably slower than with a balloon bolus tube fitted with the same gravity director-head under comparable conditions. For this reason, it seemed that if a balloon bolus is considerably more efficient than a mercury-filled condom bolus in a normal gut, it would probably be so in intestinal distention where the propulsive ability of the gut is impaired. It has been observed time and time again in cases of ileus of neurogenic or irritative origin that decompression may take as long as fifty-two hours or longer with a balloon bolus. The importance of hole design in conjunction with the balloon bolus has already been mentioned. These two factors are almost certainly responsible for the successful early decompression of so-called adynamic ileus. In these cases redistention will occur if a gastric tube is not introduced into the fundus of the stomach as soon as the intestinal tube has reached the ligament of Treitz. It is probable that in this type of case the excellent results reported by Cantor[7] were recorded in the phase of recovery from the distending mechanism as described by Devine.[11]

The Position of the Gravity Director-Head.—Here again the fundamental purpose of rapid introduction of the tube must be borne in mind. It has been found that the arrangement shown in Fig. 12, where the gravity director-head has been positioned as close to the tip of the tube as possible, is most satisfactory. This position enables the terminal holes to be pulled into the fundus of the stomach in the severe degrees of distention permitting gas injection which in turn makes possible rapid delivery of the gravity director head to the pylorus. Various other arrangements of the gravity director-head have been tried, varying from elongation of the unit (as in Fig. 9, *d*) to attachment by means of thread to a distance of six inches distal to the tube tip. It is extremely difficult to evaluate these various arrangements, but it is probable that the single advantage of the shortened-up design in making possible rapid delivery of the tube tip to the pylorus will outweigh the advantages of other arrangements.

Inflatable Boluses.—During the recent world conflict Honor and Smathers were responsible for the construction of a polyvinyl resin double-lumen tube utilizing the gravity director head which, in addition, could be inflated by means of a very small inflation passage incorporated in the wall of a tube of adequate bore for removal of intestinal contents. I have tried this arrangement and some improvements were made as shown in Fig. 10, showing the development of the inflatable gravity director-head. It will be noted that some of the later models show a separate compartment for the mercury, since it was found that where the tube was so constructed that the space above the mercury in the sack could be inflated, mercury was inclined to pass up the inflation tube and to prevent the free flow of air to and from the balloon. As a result, duodenal and intestinal contractions could not be felt with certainty. This is of minor importance where fluoroscopic control of the tube is used but is of great importance where fluoros-

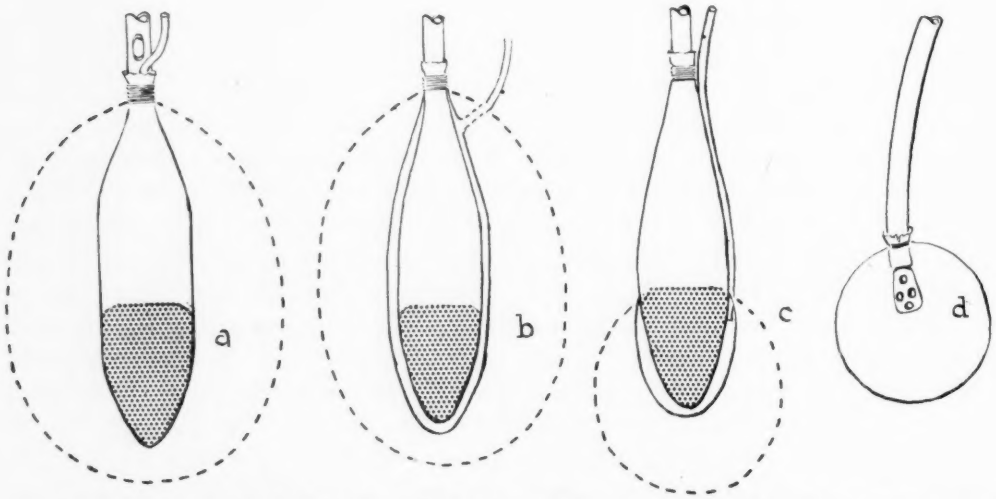


Fig. 10.—Types of inflatable gravity director heads developed and tested by the author. (*a*) A simple inflation mechanism of a standard gravity director head similar to that used in the Honor-Smathers tube. It was found that the mercury interfered with the inflation of the balloon and prevented the assessment of pyloric contractions. (*b*) A double-skinned gravity director head which overcame this disadvantage. (*c*) A further development with the tip only inflatable. This, it was thought, would aid the passage into the duodenum when the gravity director head had passed into the first part of the duodenum, but would not pass on into the second part. These were all discarded for the present design for the reasons stated in the text. (*d*) Shows an adaptation of the Miller-Abbott double-lumen tube used by Baxter Smith of the University of Minnesota Hospitals.

copy or good x-ray plate facilities are not available, since it is often possible to tell by the character of the pressure changes in the balloon whether or not the tube has entered the pylorus or duodenum. In order to overcome this difficulty, double-skinned gravity director heads were constructed so that the mercury was contained in a separate sack within the inflatable portion. With this type of construction it was possible to record pyloric and duodenal contractions reliably. The disadvantages of the inflatable gravity director head are that the bolus precedes the tube and might tend to prevent the free flow of intestinal contents to the aspiration holes situated behind; that the aspiration holes are not held in the lumen of the gut; that the position of the inflated bolus is such that it is

impossible to seal the gut proximally and to inject radiopaque substances for local bowel study or air for the purpose of unkinking the bowel should the tube become arrested. Because of the fact that the inflatable bolus is not supporting at least one or two aspiration holes in the lumen of the bowel, multilevel holes toward the extremity of the tube are necessary in order to try to obtain good drainage, thus introducing the disadvantages mentioned. This renders the rapid passage of the tube through the stomach to the pylorus by air injection, as in the technique to be described later, impossible in moderately severe cases of distention. The advantages of the inflatable gravity head are that the size of the balloon is under control from outside of the patient at all times, and that it is sometimes possible to get the gravity director head into the first part of the duodenum but not around into the second part of the duodenum so that with the design of tube with a separate balloon bolus attached near the tip of the tube as in the Miller-Abbott tube there is some delay while the partially inflated balloon bolus is carried into the duodenum by the antral pump. In this latter situation time can be saved by using the type of inflatable gravity head shown in Fig. 10, *c*. In my experience so far these advantages do not outweigh the disadvantages. The advantages of retaining the intestinal balloon in combination with the gravity director head are as follows:

1. The aspiration holes just distal to the balloon are held away from the lining membrane of the gut which permits of maximum continuous suction for removal of intestinal contents and prevents drag by adherence of gut membrane to holes.

2. The balloon is probably the best bolus for the bowel to act upon since it can be inflated to stretch the bowel wall and thus stimulate the bowel to activity.

3. The balloon can be used to seal the bowel proximal to the aspiration holes through which gas or radiopaque media can be injected.

4. In cases of postoperative distention due to adhesion where the bowel is kinked the balloon bolus will pass down the gut and re-establish continuity where the gravity director head alone will not.

The Present Design of the Author's Tube.—As a result of studying the various alternative arrangements and possible designs of tubes, I have come to the conclusion that the most generally useful design of tube at present in no way fundamentally differs from the original except in the choice of materials, and details of construction of a tube which will give a very high pass rate and which has embodied into it as many essential features as possible will be described. This design of tube has been carefully evaluated clinically by me on some 250 cases. Reference to Fig. 7 will show that a balloon bolus is tied on in a special way to a plastic tube of dimensions which have been found to give the best results. There are two terminal aspiration holes, adequately supported by a metal insert placed just in front of the point of attachment of the balloon bolus. The gravity director head is tied on to the end of the tube as the inflation tube is separately applied, as in the original built-up Miller-Abbott-Johnston tubes. It is extremely important to resist the temptation to make any holes

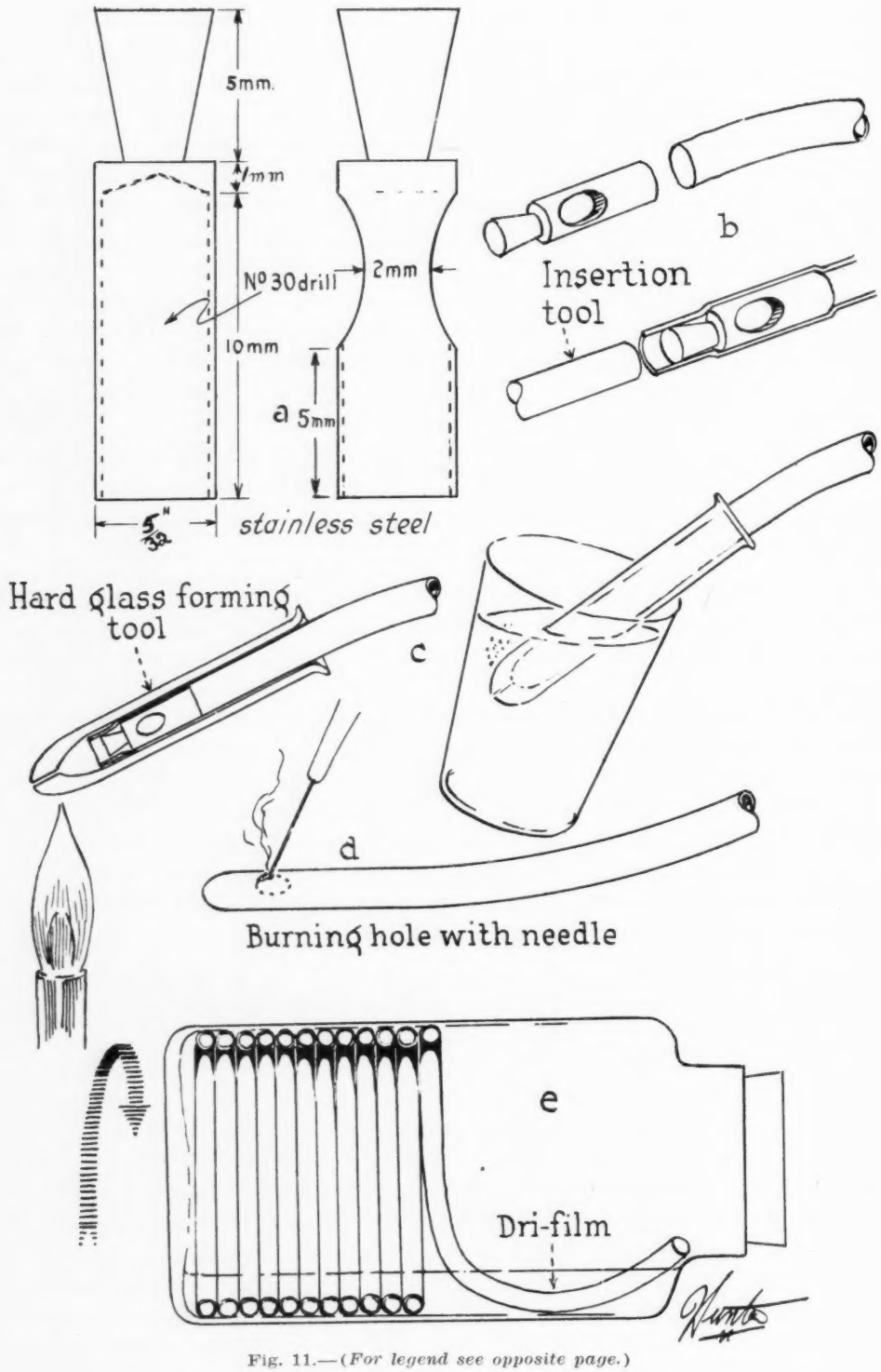


Fig. 11.—*(For legend see opposite page.)*

other than those shown, and should the problem of redistention occur, the answer is the stomach tube, placed in the fundus, made preferably with Koroseal by the method shown in Fig. 11, with continuous suction applied until recovery of the bowel.

The Future Design of Tube.—In order to obtain tubes suitable for infants and tubes of such small dimensions as to make the wearing of them by patients more comfortable, the use of a supported-wall tube is desirable. This seems to be the only way to reduce the thickness of the wall and to maintain at the same time maximum flexibility, freedom from kinking, and suction capacity. Unfortunately, the manufacture of such tubes is not easy on the laboratory scale, and so time must elapse before this very desirable method of construction can be achieved. Fig. 1 shows the type of tube envisaged by me. It will be seen that the wall is extremely thin compared with the standard tube now used, thereby achieving a better proportion between bore and outside diameter. The suction and inflation tubes will be incorporated as in my early rubber tube (Fig. 5, *No. 5*) so that the inflation tube can be easily stripped off at both ends of the tube. This will facilitate the attachment of the balloon and will permit easy visual differentiation between inflation and suction tubes at the proximal end. It will also eliminate costly and confusing metal connecting pieces as fitted to the so-called Miller-Abbott double-lumen and the Honor-Smathers tubes (Fig. 15). The suction tube will be modified with an included spiral of either metal or nylon in the wall so that a smaller outside diameter will be possible together with an even larger lumen. An easily fitted combination balloon and gravity director head assembly has been developed and is shown in Fig. 12. This is at present being used with a separate inflation tube, pending the production of a suitable double-lumen plastic tube as in Fig. 5. *No. 5*. Fig. 12, *a* shows the combination bolus before assembly. Two and one-half cubic centimeters of clean mercury are placed in the gravity director head after tying in the metal inflation connector tube as shown in Fig. 12, *a*. Next, the suction tube with its metal insert, holes and catheter end formed, is lubricated with soapy water (Fig. 12, *b*) and pushed into position. All air is expressed from the gravity director head which is then tied on with 00 Deknatel surgical silk. The balloon is turned back over and tied rubber to rubber at the metal insert, Fig. 12, *c*. Holes are cut in the latex film to correspond with those in the tube. The rubber to rubber

Fig. 11.—The method of fabrication of a satisfactory long intestinal tube with the greatest number of desirable features possible. (*a*) This is a machinist's drawing of the stainless steel metal insert which can be machined easily from stainless steel rod. The rod is mounted in the lathe and a No. 30 drill run in. Drill wander may occur, so a smaller pilot may be used. The holes are formed with a round file by eye, and then a parting tool can be used to form the conical end before parting off with the same tool. (*b*) The metal insert is pushed into the Koroseal surgical tubing of ⅛ inch bore and 3/64 inch wall thickness as shown. (*c*) The hard glass-forming tool is heated to a determined degree and the tube with metal insert pushed home. No browning of the Koroseal should occur. The tube is then immersed in cold water to set, after which the formed end can be withdrawn. (*d*) Two holes are burned to coincide with those of the metal insert and are burnished smooth at the edges with a warm needle. The needle can be cleaned in the flame and wiped on cloth. (*e*) The finished tube is coiled into a bottle containing some dri-film. The stopper is fixed in place and the bottle rotated so as to pump the dri-film throughout the length of the tube. The tube is then withdrawn vertically and allowed to drain into the bottle. The stopper is applied at once and the tube and hands immersed in running water. This brings about hydrolysis and the hydrochloric acid formed is washed away. The lumen of the tube is flushed thoroughly with water and the tube hung up to drain and dry.

tie over the metal insert insures a gas-tight joint. Koroseal is thermoplastic and a rubber-to-plastic joint is not reliable. The capacity of the balloon bolus is 5 c.c., which is enough for a recording of pyloric and duodenal contractions, after which it is distended up to 20 c.c. for passage down the bowel, and to 40 to 50 c.c. in order to seal the bowel for fluoroscopic study or for distal injection of air for releasing obstructions. By using this small capacity balloon it is possible to use a thicker latex film which makes for longer life in use.

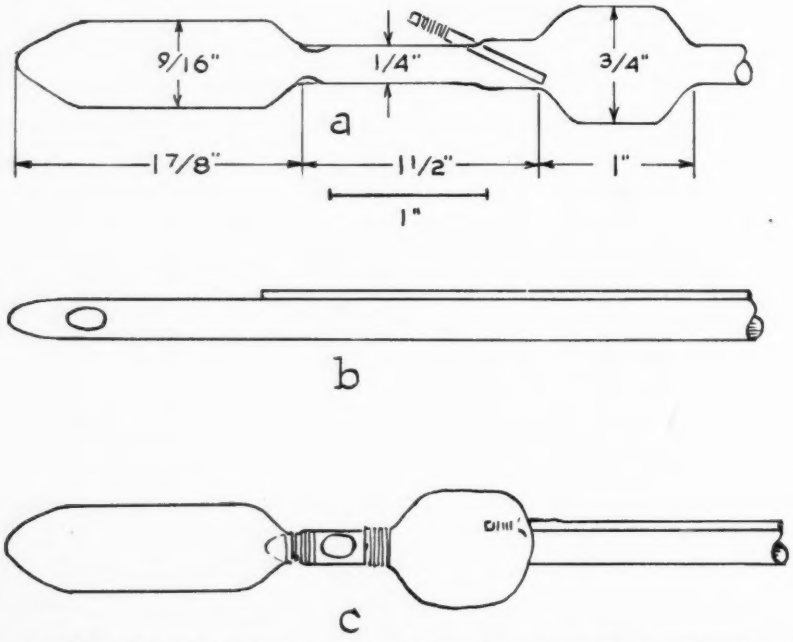


Fig. 12.—The type of long intestinal tube designed for commercial production which has been clinically tested and which has as many of the desirable features incorporated into it as is at present possible. The balloon and gravity director head assembly is shown at (*a*) as produced by latex dipping. A suitably sized needle is inserted, as shown and tied in place. Next, the load of mercury (2½ c.c.) is run into the gravity director head. Now the double-lumen tube of suitable material, with metal insert in place and hole formed *b*, is pushed into place as shown at (*c*). The needle is manipulated into the inflation lumen and the balloon turned back and tied in position. All air is expressed from the gravity director head via the aspiration hole and the neck of the gravity director head is then tied on. Last, the latex film covering the aspiration holes is picked up with forceps and cut to correspond with the aspiration holes. It will be noticed that the balloon is small. It has an undistended capacity of 5 c.c. which is sufficient to record pyloric contractions and to be carried through the pylorus should delay occur at this point. Once in the intestine it is inflated to 20 c.c. for decompression and to 40 to 50 c.c. for sealing the gut proximal to the aspiration holes should a local bowel manipulation be desirable. This design enables an extremely durable latex film assembly to be utilized without a great bulk of rubber so that many intubations are possible without renewal, provided mineral oil is not permitted to deteriorate the rubber.

PROGRESS TOWARD THE ACHIEVEMENT OF THE IDEAL TUBE

Since the introduction of the gravity director head in 1944 it has been possible to evaluate the device clinically. Improvements in design, materials, and technique of using the long intestinal tube have been gradually developed. No attempt has been made as yet to arrange for manufacture since further development seems possible. Many of the fine points concerning the design are not at first apparent, but they have been arrived at from trial and error of many possibilities, and the present design has incorporated into it as many of the desirable factors as are at present possible.

TECHNIQUE OF USE AND MANAGEMENT OF THE BUILT-UP TUBE DESCRIBED

The technique of the built-up tube is based upon considerable experience and is designed to overcome many of the difficulties which have been encountered so far. It is essentially active and designed to deliver the gravity director head to the pylorus quickly in all cases of distention save the most extreme degrees. In these latter cases the experimental gastric balloon may be tried.[5] The stages of the technique should be carried out in detail.

The following articles are required:

(1) Cotton applicators
(2) Local anesthetic (for example, 2 per cent tetracaine)
(3) Non-oily surgical lubricant
(4) A large syringe of 50 c.c. capacity with a correctly fitted plunger
(5) A free-running all-glass syringe of 20 c.c. capacity
(6) A glass of water with a glass drinking straw bent on itself at an angle of 60 degrees
(7) Cotton gauze and bandages or tape for wrapping hands of patient
(8) Assembled and tested tube
(9) A No. 17 needle with the point removed
(10) A short piece of rubber tube to fit over the plastic aspiration tube
(11) A strong pair of hemostats
(12) A screw clip
(13) Adhesive tape

No previous sedation or special medication is given. If the patient is extremely nervous, sodium amytal may be given intravenously until his cooperation is obtained, but rarely will this be found necessary. A firm but patient approach by the medical attendant should be adopted. The nature of and the reason for the procedure should be carefully explained to the patient and his cooperation in the matter of swallowing at the right time requested.

The balloon is tested for capacity and air leaks with the 20 c.c. all-glass syringe connected to the inflation tube by means of the No. 17 needle stub. Next, the gravity director head and balloon are laid just distal to the xiphoid process of the sternum and the distance from this point to the angle of the jaw and then to the external nares is marked by a small piece of tape stuck onto the tube. Thus, individual variations in the distance from the nostril to the fundus of the stomach are taken into account.

Anesthetization of the Nostril.—A cotton applicator with a generous amount of cotton twisted on is dipped in 2 per cent tetracaine and inserted in one or other nostril and pushed gently back gradually over a few minutes until the tip has reached as far back as possible. An assessment of the size of the passage can be made at the same time. If the passage is small the other side should be anesthetized and assessed in the same way.

Passage of the Tube Into the Posterior Pharynx.—The nostril is filled with non-oily surgical lubricant and a generous amount is poured onto the tip of the tube and balloon held in the hand. Then, with the patient lying on his back with no pillow, the gravity director head is milked into the nostril with the thumb and forefinger. The balloon is pushed in after it. When the two tubes are in the nostril and the gravity director head is in the posterior pharynx, the patient is placed in a sitting position and leaned well to the left with his legs over the left-hand side of the bed or table. He is told to swallow hard twice when he feels the tube tip in his throat and to pant like a dog. The tube is then held loosely in the fingers and allowed to slip down into the stomach as the patient swallows water.

Rarely in certain patients who have difficulty in swallowing, in old patients, and in overly sedated patients, it is advisable to carry out the preliminary swallowing with the patient still on his back, since the gravity director head is likely to enter the trachea. If this occurs, the patient may or may not react unusually, but upon assuming the upright position, the tube will be found not to progress downward. If it is suspected that the trachea has been entered, the tube should be pulled back to the pharynx and the patient given a short rest without being left unattended by the intubator. Then the patient should be put on his back as mentioned previously.

When the tape mark has reached the nostril, air should be pumped into the stomach through the aspiration tube with the 50 c.c. syringe to an amount not less than 500 c.c. If the patient immediately eructs, the tip of the tube is either still in the esophagus and should be passed in further, or the intra-abdominal pressure is such that the stomach cannot be inflated. It is advisable to proceed at once to the fluoroscopic table if difficulty occurs.

After injection of air the tube is passed in a further ten inches with the patient still in the vertical position. This avoids difficulty with stomach shelves and drops the gravity head to the lowest point of the stomach. The patient is then turned upon his right side and usually the gravity director head will roll over at once to the pylorus. This is confirmed by inflating the intestinal balloon with 5 c.c. of air and checking to see if this air is immediately expelled. In severely distended cases this test is unreliable since if the tube is in the esophagus the patient will feel it there and if it is in the stomach the intra-abdominal pressure will drive the air out of the balloon. The balloon is filled to 5 c.c. and allowed to deflate with the syringe held horizontally and then quickly refilled in order to stimulate the antral pump. If this is active, the piston is held down for one minute and the process repeated. After fifteen minutes of right-side lying, the patient is turned on his back and a radiograph taken with the top of the plate at the level of the axillae with the arms at right angles to the trunk. If the gravity director head is in the first part of the duodenum the balloon is filled to 5 c.c., the patient placed in a sitting position, and a further radiograph taken fifteen minutes later. If the second part of the duodenum has been reached, the tube should be pointing caudally and on the right-hand side of the vertebral column. The patient can then be placed on his left side with the

balloon still filled to 5 c.c. Continuous suction should be connected up at this point.

It is extremely important to be sure that there are no constrictions in the line from the tube to the suction bottle. Frequently glass connectors are used with extremely small orifices. The best way to insure a good joint without constriction is to slip a piece of rubber tube over the suction tube. This can be easily removed and eliminates glass connectors (Fig. 15, *c*). It also has the advantage of enabling clamping off of the tube with hemostats after inflating the stomach, since plastic tubes are damaged by clamping.

It is a great advantage to carry out the whole process with the aid of a fluoroscope. This should be used for quick glances in between manipulations. The condition of the patient is ignored in so far as transport to the fluoroscope is concerned, but the rate of working is controlled to suit the patient's reactions. Where fluoroscopy is used and the second part of the duodenum is reached, an attempt should always be made to manipulate the tip of the tube to the ligament of Treitz before returning the patient to bed. This can often be accomplished by altering the position of the patient and inflating the intestinal balloon to 10 c.c. If it is desired, the process can be carried out in bed in the ward, although it is considerably more time-consuming. A mechanical tilting table is greatly to be desired with very ill patients, so that even if a fluoroscope is not available, it is possible also to obtain first-class x-ray films with the aid of a Potter-Bucky grid.

Should it not be found possible to intubate the second part of the duodenum after placing the gravity director head at the pylorus, the patient should be placed on his right side with 5 c.c. of air in the intestinal balloon, with plenty of slack in the stomach, and with the tubes taped to the nose. In the majority of cases the tube will be found in the gut within six hours. The case should be reviewed in order to determine whether or not this delay is permissible. In transporting a patient it is advisable always to tape the tubes securely to the nose.

Once the tube is in the bowel, the intestinal balloon is inflated to 20 c.c. and orders are given to pass four inches of each of the two tubes into the nose every hour in order to maintain slack in the stomach. In cases of suspected adynamic ileus, it is advisable to tape the tube to the nose after passing in the slack, and as soon as the ligament of Treitz has been passed to install another Koroseal stomach tube into the stomach and to connect this up to another continuous suction apparatus situated on the opposite side of the bed. This seems in practice to prevent redistention. If redistention has already occurred, the tube should be withdrawn to the ligament of Treitz under fluoroscopic control and allowed to pass down again with a gastric tube in place.

The tube is cleared every hour by injecting isotonic sugar solution down the tube forcibly. Water and sodium bicarbonate should never be used. In old people, uncooperative patients, and children, the hands should be bound over a palmar pad securely and one bound hand tied to the bed. This saves a great deal of time, worry, and nursing care. Old people are sometimes very difficult to evaluate relative to cooperation and usually cannot be trusted.

Further Management.—A good radiograph should be obtained of the whole abdomen every twenty-four hours or more frequently in the initial stages, and the patient should be continually reviewed in the light of his clinical condition.

Arrest of tube in the gut: If the gravity head does not appear to have moved in two successive twenty-four hour films, the possibility of arrest should be considered. This may be due to a leaking balloon which should be emptied completely and refilled every twenty-four hours. If the balloon is found to be satisfactory, the patient should be positioned in the most favorable position for advance for twelve hours with 10 c.c. of air in the balloon and a further radiograph taken. If no change in position is recorded, the patient may be taken to fluoroscopy and an attempt made to discover the presence of an obstructing mechanism by means of a local bowel enema.[14]

Technique of local bowel enema: Some watery barium sulfate is injected down the tube after inflating the balloon 45 to 50 c.c. This size of balloon can be maintained for only a short time and as soon as the patient complains of colic the balloon should be deflated for a short time and then reinflated if desired. Ten to fifteen minutes is the usual duration of extreme distention of the balloon tolerated. The barium injection should be continued under fluoroscopic control, and if desired air can be pumped into the bowel as well. Sometimes it is an advantage, after injecting the barium sulfate, to withdraw the tube, after deflating the balloon, by pulling at the nostril while observing the tip with great care. After all slack has been taken up, the tip will suddenly jump back as the bunched bowel slips off the tube. After using barium sulfate suspension, the tube should be washed down thoroughly.

In postoperative cases where kinking of the distended bowel due to adhesions is suspected, it is possible to seal the bowel proximally and to inject gas into the bowel distally. This may unkink the bowel.

When the bowel is decompressed, the balloon should be deflated to 5 c.c. to hold the bowel lining membrane away from the aspiration holes, and suction maintained until gas is passed spontaneously per rectum. A study of the amount of aspirated fluid every twenty-four hours will usually show a sudden fall and this may indicate the resumption of bowel absorption. Suction is stopped and the patient tried on a liquid nonresidue diet.

Removal of tube: The balloon is deflated and the tube withdrawn with steady traction.

Aftercare of tube: The tube is flushed with water, taking care not to get water into the inflation tube, and left soaking in aqueous antiseptic and deodorant after having filled the lumen. The inflation tube should be taped to the edge of the container to prevent its falling into the solution.

The balloon is tested and after washing and drying, inside and out, the rubber is talced and the tube stored. The suction lumen at the metal insert should be checked for accumulations. If water gets into the inflation tube, removal is required. This entails renewal of the balloon. If mineral oil has come into contact with the rubber, renewal is necessary. Mercury collected from discarded tubes can be cleaned by expression through cloth.

It will be found that a considerable life can be obtained from Koroseal tubes. When they become too stiff at blood heat, the metal insert should be removed before discarding.

Existing Available Commercial Tubes.—

1. The so-called Miller-Abbott double-lumen tube (1938), Fig. 6, *No. 2,* is responsible for much of the confusion which has arisen concerning the value of long intestinal intubation and the consequent delay in development. The users of this tube failed often to realize its inadequacies of design and tended to use the medium-sized or even the smallest size (Fig. 5, *No. 2* and *No. 3*), since the largest size was often too large for nasal passage. Satisfactory removal of intestinal contents can be obtained only by using the largest size (Fig. 5, *No. 4*). Reference to Fig. 5 will show that the cross-section of the suction lumen of this tube is equivalent to a round bore of $\frac{3}{32}$ inch, or $\frac{1}{32}$ inch less than $\frac{1}{8}$ inch. Considerable nursing attention is necessary in order to keep the tube clear of particulate matter, especially when the intestinal contents are viscid. This inadequacy of bore is further aggravated by unnecessary length and faulty design of aspiration holes which are situated proximally to the balloon, and which require intermittent suction in order to prevent adherence of bowel lining membrane. The small perforated metal bucket attached terminally rapidly becomes clogged with particulate matter, leaving the removal of intestinal contents to the proximal holes mentioned. Injection of irrigation fluid will not clear these terminal holes, as mentioned previously, so that when the balloon bolus is inflated the intestinal contents must pass the balloon in order to reach the only functioning holes. The arrangement of aspiration holes makes it impossible to seal the bowel for the purposes mentioned before. The combination metal connecting piece outside the patient gives rise to serious faults on occasion, and air leaks occurring here are often not suspected. Confusion between suction and inflation connections (Fig. 15, *b*) can easily occur even in a good light, and results in accidents, such as the injection of barium sulfate or irrigation liquid into the balloon, with attendant dangers of necrosis of the bowel wall if this accident is not recognized and quickly corrected. Replacement of the balloon bolus by tying on requires considerable skill, especially at the proximal point, since if tied too tightly the inflation lumen is occluded, and if tied too loosely air leakage occurs. There are no metal inserts to overcome this difficulty. The tubes are made of red rubber, which, in addition to being irritating to mucous membranes, gradually stains black and picks up objectionable odor which cannot be removed. The tubes are brilliantly radiopaque. In use, the disadvantages of the Miller-Abbott double-lumen tube concern the difficulty in getting them to present to the pylorus rapidly under fluoroscopic control even when a wire stylet[12] is used. This is a complicated process and very distressing to the patient. Its performance can be greatly improved by the use of mercury as suggested by Sivertsen[15] and reported by Harris.[8] In my opinion, if the largest Miller-Abbott tube cannot be introduced into the nose it should be passed orally, with the mercury not more than 3 c.c. already inserted, as this will greatly

facilitate swallowing. Arrest at the lower end of the esophagus and in the pyloric region (Figs. 3 and 4) may be expected and should be corrected under fluoroscopic control. Almost continuous nursing attention is necessary together with an intermittent suction apparatus in order to get reasonably good results.

2. The Harris tube (1945), Fig. 6, *No. 8*, and Fig. 13, *f*, marked the advent of "simplified" intestinal decompression techniques, by the use of the single

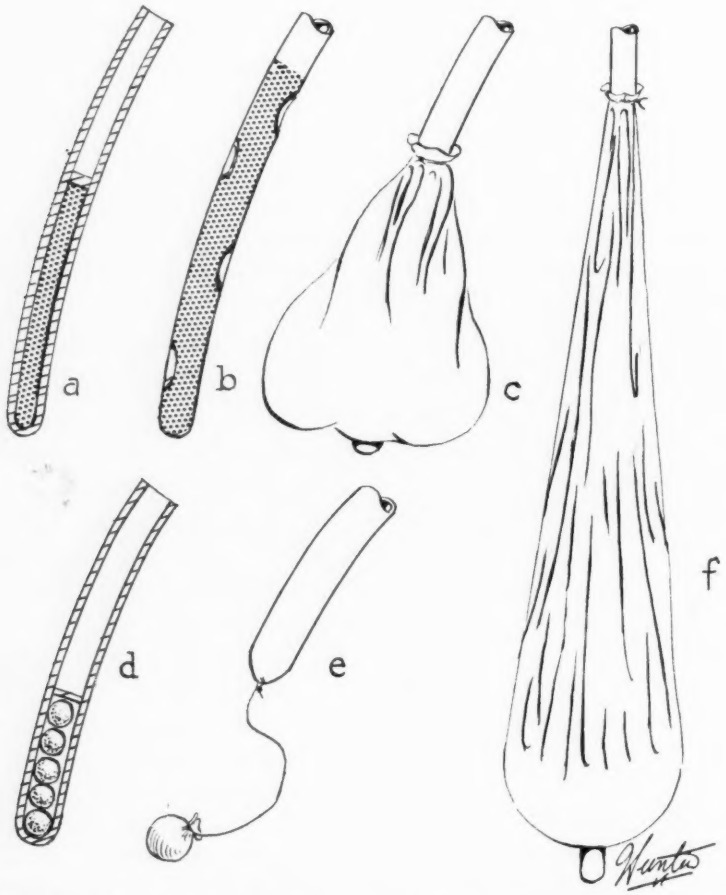


Fig. 13.—Various types of weighted tipped tubes. (*a*) Wilkins gastroduodenal tube, a rubber tube with the tip filled with mercury in a manner similar to Hurst's esophageal dilators. (*b*) The Wangensteen lead-tipped rubber tube. (*c*) The Miller-Abbott double-lumen tube loaded with mercury after passage of the tube, thus wasting the advantage of mercury as an aid for swallowing. (*d*) Rubber tube filled with lead balls (Baxter Smith). (*e*) A lead ball wrapped in rubber and tied onto the end of a rubber tube with a length of thread. also used by Baxter Smith at the University of Minnesota Hospitals. (*f*) Condom tied around a single-lumen tube and loaded with mercury before passage, by Harris.

lumen long intestinal tube. The original tube was provided with a totally inadequate suction lumen (Fig. 5, *No. 1*) which was little larger than that of the smallest Miller-Abbott tube. More recently its designer has advocated a shortening of length from the original 10 feet to 6 feet.[10] This would improve its suction efficiency but little. The original tube was made of rubber, with its attendant disadvantages. Inserts, however, were provided where the condom was tied on to avoid constricting the suction lumen at these points. The tube

has been modified[6] and an adequate suction lumen provided in a plastic material. Two condoms instead of one have been advocated by the same authors in order to minimize the risk of rupture. Harris[10] has advocated the flushing out of the condom with carbon dioxide gas before tying on in order to insure complete evacuation of air and to prevent distention of the balloon with gas after prolonged stay in the gut.

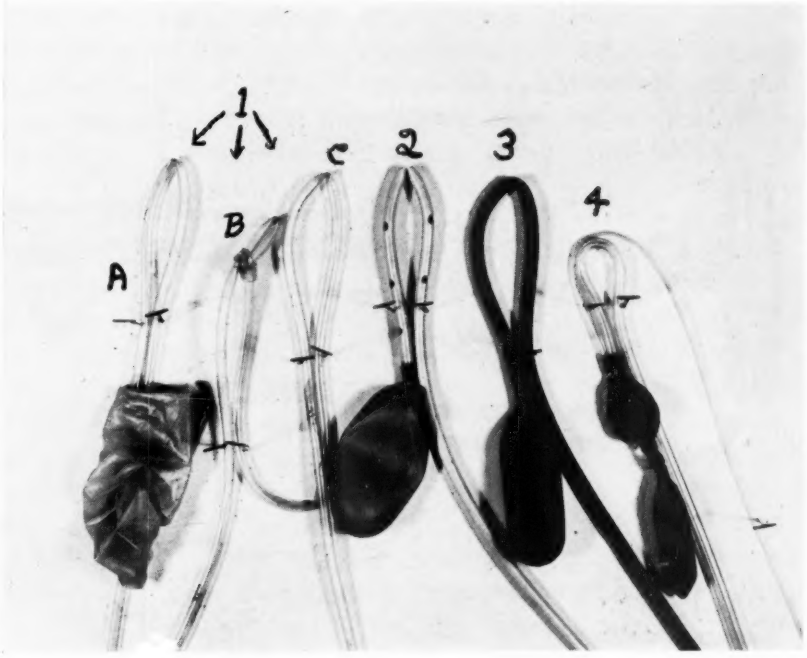


Fig. 14.—The importance of adequate wall thickness and hole design illustrated. The tubes were brought together and the loops shortened gradually. At the occurrence of kinking, pins were pressed home to fix. Note the distance of the pins from the bend in each case. *No. 1* shows the Kaslow tube; (*A*) shows the kinking which occurs easily in the region of unsupported aspiration holes; (*B*) shows complete occlusion upon knotting and pulling as tightly as will occur when in the gut; (*C*) shows kinking of the tube apart from the region of the aspiration holes. *No. 2* shows the tendency of the Honor-Smathers tube to kink in the region of the holes. *No. 3* shows the same tendency in the Cantor tube. *No. 4* shows the Koroseal tube used by the author with adequate bore and wall thickness. Note the proximity of the pins to the bend as compared to the other tubes. The lumen is still clear.

3. The Cantor tube (1946), Fig. 6, *No. 6*, was claimed as another simplified intestinal tube. It consists of a red rubber tube of adequate bore (Fig. 5, *No. 6*), a gravity director head of the shape shown in Fig. 8b and of the same thickness as that used by me. The blunt-ended condom used by Cantor has not appeared on the commercially produced tubes. The design of the holes is satisfactory when new, since the tube has an adequate wall to insure their patency. In use there is a tendency for rubber tubes to soften and result in kinking of the tube at the site of perforation (Fig. 14, *No. 3*), especially when of the dimensions used in the Cantor design. The gravity director head is large and will tend to be held up at the lower end of the esophagus or in the pyloric canal (Fig. 3,*a*). A more pointed end would help to overcome this. A more serious disadvantage of this size of gravity director head concerns the size

which it may assume should it become distended in the gut. It is not tied on but cemented, so that leakage or separation may occur. If the tube should be withdrawn intact until the gravity director head is in the pharynx, spillage of mercury and aspiration unto the lungs is a very real danger.

4. The Honor-Smathers double-lumen tube (1947) was the first commercially produced plastic tube. It has an adequate bore (Fig. 5, *No. 11*) and is fitted with an even larger gravity director head than that of Cantor (Fig. 8,*a*), which is inflated by a small airway built into the wall; thus distention is under control at all times. The designers advise the use of a stylet or forceps for introduction into the nose, and the danger of rupture and aspiration of mercury into the lungs is increased tremendously thereby. The aspiration holes

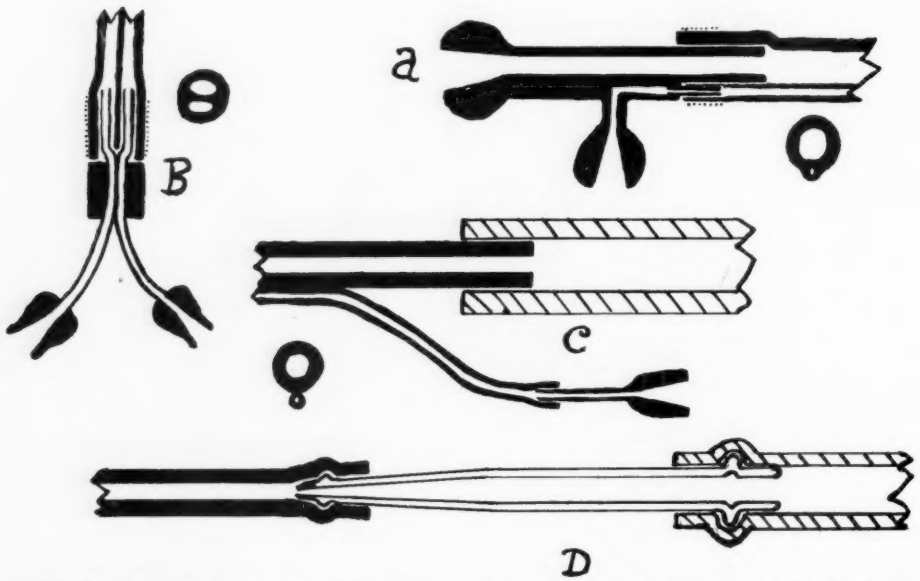


Fig. 15.—External sources of inefficiency of long intestinal tubes. *A* and *B* show the metal connection pieces (the Honor-Smathers and so-called Miller-Abbott types, respectively). Both of these are necessary in order to make satisfactory connections with the double-lumen tubes shown in section beside the drawings. They both have the disadvantage of giving rise to confusion as to which of the orifices is connected to which bore. Thus, the accidental injection of liquid into the balloon is a real danger, especially where lighting conditions are poor as in the fluoroscopic room. Of the two, the Honor-Smathers is by far the better design, since an adequate, unimpeded passage of intestinal contents to the drainage bottle is provided for and at the same time the right-angle side connection to the inflation lumen is less likely to be confused with the suction connection. Both of these connections may give rise to trouble through the leakage at the point of connection to the tube. *C* shows a simple solution. The double lumen section is so fabricated that the inflation tube can be easily stripped off from the suction lumen and a blunt needle inserted in the open end for connection to the syringe. This shape of double extrusion also makes for easy attachment of the balloon and gravity director head assembly shown in Fig. 12. The connection to the suction apparatus is easily accomplished by slipping a piece of rubber tube over the outside and in this way the flow of intestinal contents is not impeded. *D* shows an unsuitable solution which has occurred in the author's experience. The tapered glass connection piece greatly obstructs flow.

are grouped near the tip for a distance of 6 inches and are rounded, not quite full bore in diameter. No support is provided, and therefore the tube is prone to twisting and kinking, especially when the tube softens at body temperature (Fig. 14, *No. 2*). The metal connection piece (Fig. 15,*a*) is similar to that of the so-called Miller-Abbott double-lumen tube but is properly designed so as to provide a full-bore passage. Of all the available commercial tubes this is the best, though still lacking in some essential features. My modifica-

tion of this tube is shown in Fig. 6, *No. 5*, and Fig. 12. This tube tends to stiffen in use sooner than does Koroseal surgical tubing.

5. The Kaslow gastrointestinal tube[13] (1948) is shown in Fig. 6, *No. 9*, and Fig. 14, *No. 1*, and in my opinion has a number of serious faults. The section of the tube, which is constructed of polyvinyl chloride type material, is shown in Fig. 5, *No. 9*. It has a totally inadequate wall thickness. In use it will lead to kinking and obstruction of the lumen. A condom of the Harris type is used and the proximal tie is made over a semirigid collar placed over the tube. This is an advantage over the arrangement used by Harris in that is will probably leak and thus eliminate distention of the balloon. A small plastic tube, perforated, doubled upon itself is inserted into the end of the tube. It is probable that the design of this tube terminally has the same disadvantages as the metal bucket arrangement of the double-lumen so-called Miller-Abbott tube. The main holes are placed proximally to the balloon and are elongated and unsupported. Twisting and kinking is very evident as the tube is handled outside the gut in the region of the holes. The makers invite the user to tie the tube in a knot. When this is done, the result is complete occlusion upon pulling the knot as tight as it would be pulled by the intestine (Fig. 14, *No. 1B*).

Owing to the arrangement of holes, none of the available commercial tubes can be used to inflate the stomach where this is necessary in order to obtain rapid access of the tip of the tube at the pylorus in the severer grades of distention of the bowel. In addition, they cannot be used either for local barium bowel studies, or for inflation of the bowel locally in order to overcome kinking and arrest of the tube due to postoperative fibrinous adhesions. All of the commercial tubes are empyrically marked off as a guide to aid in introduction. These marks are misleading. Each case should be measured as described in order to obtain more accurate judgment of the position of the tip of the tube on the basis of length of tube introduced into the patient.

METHOD OF CONSTRUCTION OF A SATISFACTORY LONG INTESTINAL TUBE

Materials.—

9 feet of Koroseal surgical tubing, $\frac{3}{64}$ inch wall by $\frac{1}{8}$ inch bore. The most stable nontoxic blend of plasticizer available must be specified.*

9 feet of No. 18 polyvinylchloride resin tube plasticized with a stable plasticizer as mentioned.†

A metal insert (Fig. 11,*a*)

A condom with a reservoir end

A condom with a plain end

A little finger of a new No. 7 surgeon's glove

$2\frac{1}{2}$ c.c. of mercury

Some 000 Deknatel surgical silk

Dri-film No. 9987‡

*It is regretted that the type of Koroseal used by me is no longer available. Sufficient demand may influence its reappearance on the market. The type now supplied is considerably stiffer, rougher, and opaque. The smaller size of $\frac{1}{8}$ inch bore and $\frac{1}{32}$ inch wall may be found satisfactory in the present product.

†Obtainable from Irvington Varnish & Insulator Co., Irvington, N. J.

‡Obtainable from General Electric Co., Schenectady 5, N. Y.

1 piece hard glass tubing 3 inches long pulled out to a catheter end and of such a bore that the Koroseal tubing slides into it easily when the metal inset has been fitted.

1 No. 17 stainless steel needle to be cut up for small tube insert

Method of Construction.—

1. *Insertion of metal insert, closing of end of Koroseal tube, and treatment of tube with dri-film No. 9987:* The metal insert (Fig. 11,*b*) is lubricated with soap and pushed into the open end of the Koroseal tubing. The object of this insert is to prevent the Koroseal tube, which is thermoplastic, from giving when the balloon is tied on and thus obstructed the lumen at this point. The hard glass-forming tool is heated sufficiently on the very end so as just to melt the Koroseal tube when this is pushed in with the fitted metal insert (Fig. 11,*c*). If the heat is to correct a solid catheter end will be formed on the end of the tube as shown in Fig. 11,*d*. After quenching in cold water, the tube may be withdrawn.

Holes are then burned in the sides of the Koroseal tube to coincide with the holes in the metal insert (Fig. 11,*d*) by means of heating an old No. 15 steel needle to red heat. A little practice will produce very nice holes. *Do not burn in any other holes in the tube.*

The Koroseal tube is then coiled into a bottle containing some dri-film No. 9987 (Fig. 11,*e*) which has the property of removing the stickiness of the Koroseal tubing and of greatly facilitating the flow of liquid within it. This material is corrosive in that it is hydrolyzed to form hydrochloric acid. The stopper is put on firmly and the bottle is rotated so that the dri-film liquid runs through the whole length of the tube. The tube is then removed, drained, and put into water containing a little ammonia and some of this water is sucked throughout the length of the tube. It is then hung up or is wiped dry and is ready to take its part in the assembly of the tube.

2. *The tying-on of the intestinal balloon:* This is designed to obtain a gas-tight balloon in spite of the thermoplasticity of the Koroseal tube and is a little complicated. It is shown in Fig. 7. It will be noted that the balloon is constructed of a reservoir condom which is invaginated on itself on the suction tube. To it is attached one of the inflation tubes.

3. *Tying-on of the gravity director-head* (Fig. 7): The glove finger is filled with the mercury and is screwed around to exclude air. A screw clip is applied near the open end, leaving plenty of room to tie on the suction tube, and then is allowed to unscrew, thus leaving a vacuum above the mercury. There should be no air in this space above the mercury. The gravity head is then tied on to the end of the suction tube firmly, with multiple surgeon's knots doubling back and forth, and is tested by pulling. The screw clip is removed and the mercury pushed up against the bound area to check for leaks.

4. *The attachment of the gastric balloon to the standard tube:* Fig. 7*h* shows the method of construction of the gastric balloon. The plain-ended condom is closed at its open end after tying in the other inflation tube which has a piece of No. 17 needle previously inserted into its end.

The plain end is pinched up and caught with a piece of the Deknatel. This silk is loosely applied as near to the intestinal balloon mounting as possible. The tube is now assembled and ready for use. It should be tested thoroughly before use. Where the gastric balloon type is used, it is extremely important to bind the two inflation tubes onto the suction tube thoroughly for a distance of one foot with either a small rubber tube or some water-repellent tape. This can be done every two inches. Otherwise there is danger of the gravity head falling through between the tubes and forming knots if the tube is not used carefully.

SUMMARY

An effort has been made to clarify the confusion which is arising concerning the design of long intestinal tubes. My progress toward the end of achieving rapid introduction of long intestinal tubes into the bowel and rapid decompression of the distended bowel is described, in the hope that designers will in the future be fully aware of the problems involved. The method of construction of an intestinal tube having as many of the desirable features as are at present possible is described. Emphasis is laid upon the necessity of using two terminal holes placed just distal to a balloon bolus for good results. A technique which will give a very high and rapid pass rate to the pylorus, especially under fluoroscopic control, in all cases is described. The lines of further development are indicated.

REFERENCES

1. Wangensteen, O. H.: The Early Diagnosis of Acute Intestinal Obstruction With Comments on Pathology and Treatment. With a Report of Successful Decompression of Three Cases of Mechanical Bowel Obstruction by Nasal Catheter Suction Siphonage, West. J. Surg. **40**: 1. 1932; also Tr. West. S. A., 1931.
2. Abbott, W. O., and Johnston, C. G.: Intubation Studies of the Human Small Intestine—A Non-Surgical Method of Treating, Localizing and Diagnosing the Nature of Obstructive Lesions, Surg., Gynec. & Obst. **66**: 69, 1938.
3. Wild, J. J.: Preliminary Report of the Use of the Gravity Director Head in Achieving Rapid Intubation of the Human Duodenum, 1945. (Unpublished.)
4. Wild, J. J.: Apparatus for Intestinal Intubation, Brit. M. J. **1**: 815, 1944.
5. Wild, J. J.: The Stomach as a Cause of Difficulty in Intubating the Human Duodenum With Introduction of the Use of the Gastric Balloon, SURGERY **24**: 70-78, 1948.
6. Herrera, R. E., Millet, J. B., and Lawrence, G. H.: A Report on the Use of the Harris Tube, Surg., Gynec. & Obst. **85**: 604-606, 1947.
7. Cantor, Meyer O.: A New Simplified Intestinal Decompression Tube, Am. J. Surg. **72**: 137-142, 1946.
8. Harris, Franklin I.: A New Rapid Method of Intubation with the Miller-Abbott Tube, J. A. M. A. **125**: 784-785, 1944.
9. Harris, Franklin I.: Intestinal Intubation in Bowel Obstruction: Technique With a New Single Lumen Mercury Weighted Tube, Surg. Gynec. & Obst. **81**: 671-678, 1945.
10. Harris, Franklin I., and Gordon, M.: Intestinal Intubation in Small Bowel Distension and Obstruction; Further Experience With the Single Lumen Mercury Weighted Tube and Analysis of Complications, Surg., Gynec. & Obst. **86**: 647-658, 1948.
11. Devine, John: A Concept of Paralytic Ileus, Brit. J. Surg. **34**: 158-179, 1946.
12. Abbott, W. O.: Indications for Use of the Miller-Abbott Tube, New England J. Med. **225**: 641-646, 1941.
13. Kaslow, A. L.: A New Material and Tube Design in Gastro-Intestinal Intubation, Surgery. **23**: 293-297, 1948.
14. Boon, T. H.: Intubation of Small Intestine. Demonstration and Localization of Partially Obstructive Lesions, Lancet, **238**: 7-10, 1940.
15. Wangensteen, O. H.: Intestinal Obstructions, ed. 2, Springfield, Ill., 1942, Charles C Thomas, Publisher.

ANNOUNCEMENT

The Samuel D. Gross Prize

The Philadelphia Academy of Surgery announces that essays will be received until Jan. 1, 1950 in competition for the Samuel D. Gross prize of $1,500. The conditions annexed by the testator are that the prize "shall be awarded every five years to the writer of the best original essay, not exceeding 150 printed pages, octavo, in length, illustrative of some subject in Surgical Pathology or Surgical Practice founded upon original investigations, the candidates for the prize to be American citizens."

It is expressly stipulated that the competitor who receives the prize shall publish his essay in book form, and that he shall deposit one copy of the work in the Samuel D. Gross Library of the Philadelphia Academy of Surgery, and that on the title page it shall be stated that the essay was awarded the Samuel D. Gross Prize of the Philadelphia Academy of Surgery.

The essays, which must be written by a single author in the English language, should be sent to the "Trustees of the Samuel D. Gross Prize of the Philadelphia Academy of Surgery, care of the College of Physicians, 19 South 22nd Street, Philadelphia," on or before Jan. 1, 1950.

Each essay must be typewritten, distinguished by a motto, and accompanied by a sealed envelope bearing the same motto, containing the name and address of the writer. No envelope will be opened except that which accompanies the successful essay.

The Committee will return the unsuccessful essays if reclaimed by their respective writers, or their agents, within one year.

The Committee reserves the right to make no award if the essays submitted are not considered worthy of the prize.

JOHN H. GIBSON, JR., M.D.
ELDRIDGE L. ELIASON, M.D.
CALVIN M. SMYTH, M.D. (Chr.)
Trustees

...a product

serving many purposes

Short-acting Nembutal also is a product that serves many purposes. More than 44 effective uses for it have been described in over 480 published reports. Clinical experience during the past 19 years has shown that adjusted doses of short-acting Nembutal can bring about any desired degree of cerebral depression—from mild sedation to deep hypnosis. Dosage required is only about *one-half* that of many other barbiturates. Small dosage means (1) less drug to be inactivated; (2) shorter duration of effect; (3) wide safety margin; (4) less possibility of barbiturate "hangover," and (5) definite economy to the patient. Shown at right is a partial list of indications for short-acting Nembutal. A glance at it may suggest new ways in which you can use the drug. Write for the new booklet "44 Clinical Uses for Nembutal." ABBOTT LABORATORIES, North Chicago, Illinois.

In equal oral doses, no other barbiturate combines **QUICKER, BRIEFER, MORE PROFOUND EFFECT** than ... **Nembutal®**

(Pentobarbital, Abbott)

Have you tried EPHEDRINE AND NEMBUTAL CAPSULES AND NEMBU-FEDRIN® CAPSULES *for the symptomatic relief of bronchospasm in certain cases of hay fever and asthma?*

44 of Nembutal's Clinical Uses

sedative

Cardiovascular
Hypertension[1]
Coronary disease[1]
Angina[1]
Decompensation
Peripheral vascular disease

Endocrine Disturbances
Hyperthyroid
Menopause—female, male

Nausea and Vomiting
Functional or organic disease (acute gastrointestinal and emotional)
X-ray sickness
Pregnancy
Motion sickness

Gastrointestinal Disorders
Cardiospasm[2]
Pylorospasm[2]
Spasm of biliary tract[2]
Spasm of colon[2]
Peptic ulcer[2]
Colitis[2]
Biliary dyskinesia

Allergic Disorders
Irritability
To combat stimulation of ephedrine alone, etc.[3,1]

Irritability Associated With Infections[4]

Restlessness and Irritability With Pain[5,4]

Central Nervous System
Paralysis agitans
Chorea
Hysteria
Delirium tremens
Mania

Anticonvulsant
Traumatic
Tetanus
Strychnine
Eclampsia
Status epilepticus
Anesthesia

hypnotic

Induction of Sleep

obstetrical

Nausea and Vomiting
Eclampsia
Amnesia and Analgesia[6]

surgical

Preoperative Sedation
Basal Anesthesia
Postoperative Sedation

pediatric

Sedation for:
Special examinations
Blood transfusions
Administration of parenteral fluids
Reactions to immunization procedures
Minor surgery

Preoperative Sedation

Nembutal alone or
[1]Glucophylline® and Nembutal,
[2]Nembutal and Belladonna,
[3]Ephedrine and Nembutal,
[4]Nembudeine®,
[5]Nembutal and Aspirin,
[6]with scopolamine or other drugs.

ANOTHER MOSBY BOOK

OPERATING ROOM TECHNIQUE

By EDYTHE LOUISE ALEXANDER, R.N., Supervisor of the Operating Rooms of The Roosevelt Hospital, New York City. Formerly Supervisor of Operating Rooms, Mountainside Hospital, Montclair, New Jersey; Supervisor of Private Pavilion Operating Rooms, New York Hospital, New York.

SECOND EDITION 768 pages, 670 illustrations. $10.00

¶ Surgery is a dramatic branch of medicine, and the past few years have seen radical changes in its methods. To keep pace with these changes and in view of the many new problems brought to the author by surgeons, operating room supervisors, and nurses, this Second Edition has been prepared.

¶ Fundamental principles and the methods of operating room technique are fully described and illustrated. The procedures are presented in a detailed manner to provide a guide for the student and suture nurses. An outline for a series of lectures on operating room technique is included, with a set of questions. As an aid to the supervisor, there are suggestions for the administration of operating rooms and a method for grading student nurses' work.

¶ New methods of preparation, sterilization of supplies, sutures and materials for operative use are emphasized. Due to the recent advances in surgery, many additional operations have been described in each section. In many instances, a brief description of the anatomy involved precedes the step-by-step description of the operation and of the instruments needed for each step. Comprehensive illustrated lists are given of instruments required for the various operations. The various types of instruments are fully described and methods for their care and sterilization are presented.

CONTENTS . . . . . .

GENERAL ARRANGEMENTS OF AN OPERATING ROOM FOR GENERAL SURGERY
CARE AND CLEANING OF THE OPERATING ROOMS
NURSING PERSONNEL OF THE OPERATING ROOM
HISTORY OF ASEPSIS
STERILIZATION
WOUND HEALING, TREATMENT, AND PREPARATION OF OPERATIVE AREAS
THE CARE AND STERILIZATION OF EQUIPMENT
SUTURE MATERIALS
ANESTHESIA
STANDARDIZATION OF DUTIES AND PRECAUTIONS
SURGICAL POSITIONS
DRAPING OF THE OPERATIVE FIELD
INSTRUMENTS, NEEDLES, AND SUTURE MATERIAL
NOSE, MOUTH, THROAT, AND NECK OPERATIONS
CHEST OPERATIONS
ABDOMINAL INCISIONS
DIGESTIVE SYSTEM
SMALL INTESTINE
LIVER, GALLBLADDER, BILE DUCT, PANCREAS AND SPLEEN
LARGE INTESTINE
LOWER SIGMOID, RECTUM AND ANAL REGION
GENITOURINARY SYSTEM
OPERATIONS UPON THE GENITOURINARY SYSTEM
VAGINAL GYNECOLOGIC OPERATIONS
ABDOMINAL GYNECOLOGIC OPERATIONS
RECONSTRUCTIVE SURGERY OF BONES, JOINTS AND TENDONS
OPERATIONS ON THE SPINAL CORD
VASCULAR OPERATIONS

The C. V. Mosby Company, 3208 Washington Blvd., St. Louis 3, Mo. MJ

Please send me a copy of Alexander's OPERATING ROOM TECHNIQUE—The price is $10.00.

☐ Enclosed find check. ☐ Charge my account.

Name _____

Address _____

For the Surgeon, the Post-Graduate Student and the Investigator

EXPERIMENTAL SURGERY INCLUDING SURGICAL PHYSIOLOGY

Second Edition

By J. MARKOWITZ, Ph.D.

Department of Physiology, University of Toronto

The author presents physiological explanations for even the simplest steps in a given surgical procedure. The fundamental technique of many standard surgical operations is clearly described, and in most cases it is applicable to human as well as animal surgery.

The second edition takes into consideration the fact that experimental surgery is now a respected and orthodox branch of instruction in medical schools. The author writes as an experimentalist, and as such regards experimental surgery as a branch of physiology. He has prepared a comprehensive and inspiring text. Students and teachers will find it invaluable since the most effective teaching of surgery today requires a familiarity with the aims, principles and accomplishments of laboratory experimentation.

550 pages, 330 figures, $7.00

SANS TACHE

THE WILLIAMS & WILKINS COMPANY

Mt. Royal & Guilford Aves. Baltimore 2, Maryland

Please send Markowitz: Experimental Surgery, $7.00

Name _____

Address _____

ANOTHER MOSBY BOOK

CANCER *of the Esophagus and Gastric Cardia*

Edited by

GEORGE T. PACK, B.S., M.D.

New York, N. Y.

Clinical Professor of Surgery, New York Medical College; Attending Surgeon, the Memorial Hospital for Cancer and Allied Diseases

192 Pages *Illustrated* *Price, $5.00*

The symposium which comprises this book originally appeared in the June, 1948, issue of SURGERY. Many requests were received to have it issued as a monograph, and as such it embodies the most recent and most notable achievements in the treatment of cancers of the esophagus.

CONTENTS

Introduction. George T. Pack, M.D., New York City.

The Roentgen Diagnosis of Cancer of the Cardiac Region of the Stomach. Robert S. Sherman, M.D., New York City.

Preoperative, Operative, and Postoperative Care in Esophageal Resections. Herbert C. Maier, M.D., New York City.

Cancer of the Cervical Esophagus. William L. Watson, M.D., New York City; and John L. Pool, M.D., New York City.

Progress in the Surgical Treatment of Carcinoma of the Esophagus and Upper Stomach. John H. Garlock, M.D., New York City.

The Use of the Roux Y in Extending the Operability of Carcinoma of the Stomach and of the Lower End of the Esophagus. John T. Reynolds, M.D., Chicago, Ill.; John P. Young, Jr., M.D., Chicago, Ill.

Surgical Treatment of Cancers of the Gastric Cardia. George T. Pack, M.D., New York; Gordon McNeer, M.D., New York.

Cardioesophageal Cancers Treated Via the Transthoracic and Transdiaphragmatic Route. Felix de Amesti, M.D., Santiago, Chile; Eliseo Otaiza, M.D., Santiago, Chile.

Subtotal Esophagectomy and Esophagogastrostomy for High Intrathoracic Esophageal Lesions. Michael E. DeBakey, M.D., New Orleans, Louisiana; Alton Ochsner, M.D., New Orleans, Louisiana.

Combined Left Abdominal and Right Thoracic Approach to Resection of Esophageal Neoplasms. Joseph E. Macmanus, M.D., Buffalo, New York.

The Treatment of Carcinoma of the Esophagus and Cardiac End of the Stomach by Surgical Extirpation. Richard H. Sweet, M.D., Boston, Mass.

Transthoracic Gastric Resection for Lesions of the Cardia of the Stomach and Middle and Lower Portions of the Esophagus. Frank S. Ashburn, M.D., Rochester, Minn.; John H. Payne, M.D., Cincinnati, Ohio; and O. Theron Clagett, M.D., Rochester, Minn.

ORDER FORM

THE C. V. MOSBY COMPANY
3207 WASHINGTON BLVD.
ST. LOUIS 3, MISSOURI

MJ

Please send me Pack's CANCER of the Esophagus and Gastric Cardia—
The price is $5.00

____Enclosed find check. ____Charge my account.

Name _____

Address _____

PROCEEDINGS of the THIRD AMERICAN CONGRESS on OBSTETRICS and GYNECOLOGY

St. Louis, September 8-12, 1947

Sponsored by The American Committee on Maternal Welfare

This comprehensive volume will make available to you the entire Proceedings of the first AMERICAN CONGRESS on OBSTETRICS and GYNECOLOGY to be held since the end of the war.

More than threescore representative papers and discussions by such eminent authorities as Adriani, New Orleans; Allen, Chicago; Baer, Chicago; Baptisti, Hagerstown; Brewer, Chicago; Brown, Iowa City; Calkins, Kansas City; Carter, Duke University; Cosgrove, New York; Davis, University of Chicago; Douglass, U. of Maryland; Eastman, Johns Hopkins Medical School; Faulkner, Cleveland; Greenhill, Chicago; J. A. Hardy, Jr., St. Louis; Jamison, Saranac Lake; Jenson, St. Louis; Kurzrok, New York City; Meigs, Boston; Mengert, Dallas; Novak, Baltimore; Philpott, Montreal; Plass, Iowa City; Potter, Chicago; Randall, Rochester; Reis, Chicago; Rock, Boston; Schmitz, Chicago; Schumann, Philadelphia; Thompson, Los Angeles; Walters, New York; Waugh, Rochester; White, Boston, and Williams, Philadelphia. George W. Kosmak, editor.

Timely, inclusive consideration of such subjects as Anesthesia and Analgesia in Obstetrics; Treatment of Cervical Carcinoma; Cesarean Section; Toward Better Maternal and Newborn Care; Sterility and Infertility; Emotional Aspects of Pregnancy; Toward Meeting Total Needs of the Maternity Patient; Pregnancy Complications; Education in Maternity Nursing; Recent Advances in Endocrinology; Abortion; Asphyxia; Myoma; Prolonged Labor; Early Ambulation; Adolescence, Genital Relaxations; Ovulation; Menopause; Cystic Ovaries; Uterine Bleeding; Nutrition; Geriatric Gynecology; Endometriosis and Erythroblastosis.

Calculated to serve as a current reference work covering the entire field of clinical obstetrics and gynecology, as well as a complete, accurate record of the Proceedings of the Congress. ● Essential in the libraries of obstetricians, gynecologists, general practitioners, other medical specialists; nurses, hospital administrators, public health workers, educators, and others interested in maternal welfare and the protection of the fetus and the newborn. ● 432 pages, 7" x 10½", illustrated, embossed, blue clothbound. Price **$9.00.**

LIMITED EDITION—ORDER NOW TO ENSURE PRIORITY DELIVERY

ORDER FORM **To Western Journal of Surgery Publishing Company.**
302 Phoenix Building, Portland 4, Oregon.

Herewith is my order for ..... (copy, copies) of the Proceedings of the Third American Congress on Obstetrics and Gynecology—1947. I enclose $9.00 covering prepublication cost per volume, including U. S. Postage.

Name.....

Address.....

.....

Please type or handletter and mail today.

Just Released!

Speed-Smith's

SECOND EDITION OF CAMPBELL'S

OPERATIVE ORTHOPEDICS

By J. S. SPEED, M.D., and HUGH SMITH, M.D.

Both of Memphis, Tennessee

SECOND EDITION. 1729 pages, 1141 illustrations, 2 color plates. IN TWO VOLUMES. Price, $30.00.

COLLABORATORS

H. B. BOYD, M.D., J. F. HAMILTON, M.D., A. J. INGRAM, M.D., R. A. KNIGHT, M.D., M. J. STEWART, M.D., and T. L. WARING, M.D., of the Staff of the Campbell Clinic and Faculty of the University of Tennessee.

FRANCIS MURPHEY, M.D., Associate Professor of Neurosurgery, University of Tennessee, Memphis; D. B. SLOCUM, M.D., Eugene, Oregon; and M. N. SMITH-PETERSEN, M.D., Boston, Massachusetts.

With the publication of this New Second Edition of OPERATIVE ORTHOPEDICS, the Mosby Company brings you the only important work in this field of medicine. It is a compilation of all previous and contemporary operative orthopedic technic—and in its new two-volume form it assumes monumental proportions.

The authors have deviated as much as possible from the concise style in the first edition. The first edition was written in a brief format, assuming that the reader could supplement preliminary sketchy discussions with his own personal experience. In this edition the editors have written primarily for the fellowship man or resident, keeping in mind the limits of his experience. They have assiduously set forth preliminary data where it was deemed necessary to apply properly certain surgical technics. To accomplish this aim, less than one-half of the manuscript is preserved in its original form from the first edition. One-third of the illustrations have been eliminated and replaced by twice their number. Three new chapters—Preoperative and Postoperative Care, Peripheral Nerve Injuries, and Amputations—have been added.

New sections have been written on Mold Arthoplasty, Ruptured Intervertebral Discs, and Difficult and Unusual Nonunions.

Order Form

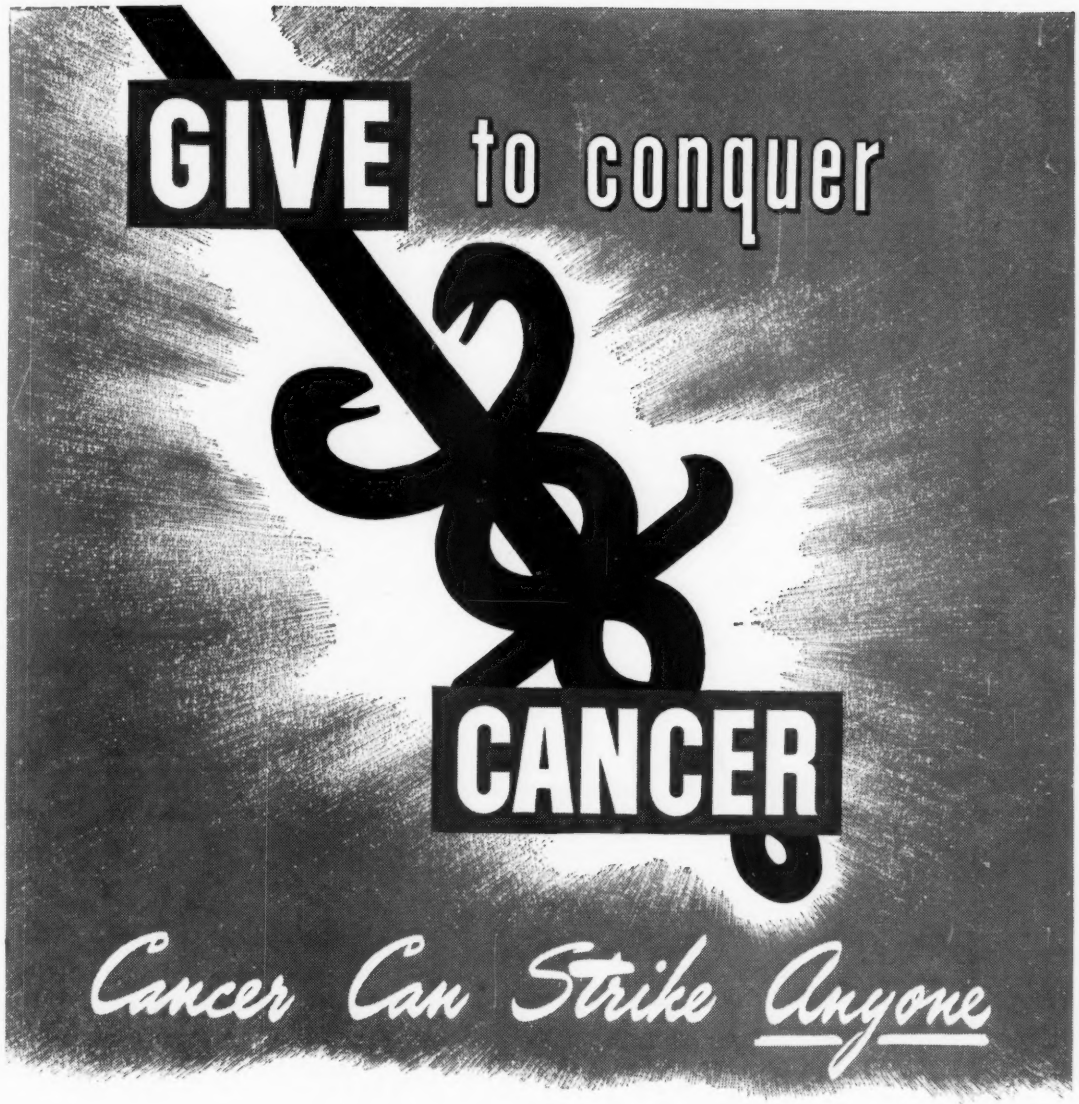
THE C. V. MOSBY CO. M. J.
3207 Washington Blvd., St. Louis 3, Mo.

Please send Speed-Smith's Second Edition of "Campbell's Operative Orthopedics." In Two Volumes. Price, $30.00.

☐ Enclosed find check.
☐ Charge my account.

Name _____

Address _____



Give and keep giving to help science defeat the disease that strikes, on the average, one out of every two homes in America. Say to yourself . . . *here is life-giving money to help those stricken by Cancer to live again.*

EVERY NICKLE AND DIME *I give helps support an educational program teaching new thousands how to recognize Cancer and what to do about it.*

EVERY QUARTER *I give helps set up and equip new research laboratories where scientists are dedicating their lives to find the cause—and cure of Cancer.*

EVERY DOLLAR *I send helps buy new equipment, helps establish new facilities for treating and curing Cancer, both still pitifully scarce in this country . . .* Guard those you love! Give to conquer Cancer!

AMERICAN CANCER SOCIETY

JUST MAIL IT TO "CANCER"

Give as generously as you can—today. Your check or money order in an envelope addressed to "Cancer", care of your local post office, will be delivered to the American Cancer Society office in your state.

Here's my $.....to help conquer cancer

NAME.....

ADDRESS.....

CITY.....ZONE.....STATE.....

INDEX TO ADVERTISERS

Please mention "SURGERY" when writing to our advertisers—It identifies you

Abbott Laboratories (Nembutal) ------ 13
American Cancer Society ------ 19

Back Copies Wanted ------ 8

Ciba Pharmaceutical Products, Inc. (Metandren Linguets) ------ 1
Crescent Surgical Sales Co., Inc. (Surgical Blades) ------ 8

Davis & Geck, Inc. (Sutures) ------ 3

Eaton Laboratories, Inc. (Furacin Soluble Dressing) ------ 4

Hoffmann-La Roche, Inc. (Berocca-C) ------ Fourth Cover

Lilly and Company, Eli (Dolophine Hydrochloride) ------ 12

Ohio Chemical & Mfg. Company (Operating Tables) ------ 2

Pratt, Waldo Todd (Handsharpener with Blue Cake) ------ 8

Sklar Manufacturing Company, J. (Surgical Instruments) ------ 9
Swift & Company, (Strained Meats) ---- 11

Western Journal of Surgery Publishing Company ------ 17
Williams & Wilkins Company, The (Books) ------ 15
Winthrop-Stearns, Inc. (Zephiran Chloride) ------ 7
Wyeth Incorporated (Testosterone) ---- 5

All possible care is exercised in the preparation of this index. The publishers are not responsible for any errors or omissions.

Key and Conwell's

4th Revised Edition

FRACTURES, DISLOCATIONS AND SPRAINS

- More than 200 new illustration added and substituted.
- All recent developments in theory and practice included.
- Section on war wounds revised especially with regard to skeletal fixation and chemotherapy.
- Complete revision of the chapter on Injuries of the Spine. Davis contributes a description of his gravity suspension method for the treatment of compression fractures of the spine and the section on cervical fractures and dislocations.

By John Albert Key, B.S., M.D., and H. Earle Conwell, M.D., F.A.C.S.

1300 pages Price, $15.00 1316 illustrations

THE C. V. MOSBY COMPANY — Publishers — ST. LOUIS 3, MO.